RAPID-PROTECTION: AN ADAPTIVE CLINICAL TRIAL OF AZD7442 AND SARS-COV-2 VACCINATION IN IMMUNOSUPPRESSED PATIENTS HIGHLY VULNERABLE TO INFECTION WITH SARS-COV-2 VIRUS

PROTOCOL VERSION V5.0

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's Standard Operating Procedures. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor:	**Cardiff University**	
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Signature	See e-mail dated 25/05/2023	**Date:** 25/05/2023
Chief Investigator:	Dr Mark Tuthill	
Signature:	See e-mail dated 24/05/2023	**Date:** 24/05/2023

General Information This protocol describes the RAPID-PROTECTION clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The RAPID-PROTECTION trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the RAPID-PROTECTION Trial Management Group (TMG). For **all queries** please contact the RAPID-PROTECTION team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

Main Trial Email:	RAPID-PROTECTION@cardiff.ac.uk	
Trial Statistician:	Catharine Porter	E-mail: RAPID-PROTECTION@cardiff.ac.uk
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Registration and randomisation:

Randomisation
Patient Randomisation for this trial will be through the use of a web-based system: https://trials.cardiff.ac.uk/portal **Details of how to access the system will be supplied to Investigators as part of the trial set-up.** **If any problem with the web-based system or it is unavailable, please contact the trial team:** **RAPID-PROTECTION@cardiff.ac.uk**

Queries:

Queries
All queries related to the trial will be emailed to: **RAPID-PROTECTION@cardiff.ac.uk**

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to CTR Safety team within 24 hours of becoming aware of the event (see section 14 for more details). **Serious Adverse Event (SAE) email address:** **CTR-Safety@cardiff.ac.uk** **Serious Adverse Event (SAE) Fax number:** **+44 (0)203 0432 376**

Contents

Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTC	Common Toxicity Criteria
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
DSUR	Development Safety Update Report
ECMO	Extracorporeal Membrane Oxygenation
ECOG	Eastern Cooperative Oncology Group
EudraCT	European Clinical Trials Database
FBC	Full blood count
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International Unit
LFT	Liver function test
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicine and Healthcare products Regulatory Agency
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NIV	Non-invasive Ventilation

OVC	Oxford Vaccine Centre
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea and electrolytes
WHO	World Health Organisation
w/v	Weight per volume

1. Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
n/a	1.1	26/05/2022	Minor amendments to include correction of typographical and formatting errors, minor clarification to some of the inclusion and exclusion criteria, and a minor update to the procedure for nasal PCR swabs for SAR-CoV-2.
n/a	1.2	11/07/2022	Removal of use of vaccine booster lists for identifying eligible participants. Time between study vaccine booster and repeat vaccination with any SARS-CoV2 vaccinations used within the study decreased from 6 months to 3 months.
1	2.0	15/08/2022	Removal of AZ vaccine arm. Increase dose of Evusheld from 300 to 600mg.
2	3.0	14/09/2022	Replacement of Comirnaty and Spikevax vaccines with their respective bivalent versions (Comirnaty bivalent (Original/Omicron BA.1) and Spikevax bivalent (Original/Omicron)). Removal of exclusion criteria no longer applicable. Clarification of vaccine booster supply. Reference to patients who may be referred from their GP/secondary care site.
3	3.1	19/12/2022	Lateral flow tests for all routine asymptomatic SARS-CoV-2 tests for subset of participants at Oxford (PCR swabs will only be taken from patients who test positive for SARS-CoV-2 infection).

			Addition of a routine SARS-CoV-2 test at the Day 56 visit for a subset of participants at Oxford. Removal of Day 42 assessments and visit for all participants.
4	4.0	09/01/2023	Amend administration guidance for AZD7442 to allow for AZD7442 to be administered as either 2 x 3mL intramuscular injections or 4 x 1.5mL intramuscular injections. Minor clarifications to eligibility criteria, including better labelling of sub-cohorts throughout. Changes to the Analysis section to better reflect the statistical analysis plan (SAP). Addition of appendix 3 to aid with data entry for participants in the haematological cohort.
5	5.0	09/05/2023	Follow-up period reduced from 12 months to 6 months. The Day 273 and 364 visits are now no longer required. Since Day 180 will now be the final follow-up visit, the safety blood sample (FBC, U&E, LFT and bone profile) that was originally included on Day 364 has been included on the Day 180 visit. Section 13.1.1 to provide instruction to provide all existing patients with the Changes to Follow up Notification form to notify them of the reduction in follow up.

2. Synopsis

Short title	RAPID-PROTECTION
Clinical phase	Phase II
Funder and ref.	AstraZeneca
Trial design	Multi-centre, interventional, open label, trial with cohorts of immunocompromised participants treated with AZD7442. Patients will then be randomised to receive an approved vaccine booster 28 days after initiation of AZD7442 treatment.
Trial participants	Patients with immunosuppressive conditions that are highly vulnerable to SARS-CoV-2 infection and have one of the following diseases: Haematological malignancies, solid tumours, renal and hepatic disorders, and inflammatory disease
Planned sample size	350 participants
Planned number of sites	5
Inclusion criteria	**All participants** 1. Provide written informed consent. 2. Previously completed SARS-COV-2 vaccinations given as part of standard care at the time of enrolment. 3. Able and willing (in the Investigator's opinion) to comply with all trial requirements. 4. Willingness to practice continuous effective contraception during the first 3 months of the trial and if appropriate, a negative pregnancy test on the day of screening. 5. Provide access to all medical records with respect to current and past medical treatments. 6. Have one or more of the following eligible conditions. 7. Adults ≥18 years <u>Cohort 1: Haematological malignancies</u> Patients with a diagnosis of haematological malignancies (within the last 5 years) and • Cohort 1a - Patients receiving active therapy with immunosuppressive or immunomodulating agents including: ○ B-cell targeted therapies (rituximab or other anti-B-cell Ab therapy) used either as monotherapy or in combination with cytotoxic therapy in lymphoma / chronic lymphoproliferative disorders OR

- JAK inhibitors (ruxolitinib or equivalent) in myeloproliferative neoplasms (MPNs)

OR

- ImiD drugs (thalidomide, lenalidomide, pomalidomide or equivalent) in myeloma and other plasma cell dyscrasias

OR

- BTK inhibitors (ibrutinib or equivalent) in chronic lymphocytic leukaemia / chronic lymphoproliferative disorders

OR

- Treatment within 24 months with lymphodepleting agents followed by chimaeric antigen receptor (CAR) T-cell therapy for any haematological malignancy

- Cohort 1b - Patients receiving aggressive therapy expected to cause temporary ablation of immune function including:
  - Acute leukaemia (AML or ALL) being treated with curative intent using intensive combination chemotherapy schedules (excluding acute promyelocytic leukaemia)

OR

- Patients within 24 months of receipt of allogeneic stem cell transplant or receiving systemic immunosuppression for graft versus host disease.

<u>Cohort 2: Solid Tumours</u>

- Early (cohort 2a) or advanced cancer (cohort 2b) (solid organ) undergoing systemic cancer treatment

<u>Cohort 3: Renal/hepatic disorders</u>

<u>Cohort 3a -Renal Disorders:</u>

Patients with kidney disease who fall into one of the following groups:

- Currently receiving immunosuppression
- Dialysis – including in-centre and home haemodialysis, peritoneal dialysis
- Transplant recipient receiving immunosuppression

<u>Cohort 3b - Hepatic disorders:</u>

- Patients with liver cirrhosis, autoimmune liver disease and liver transplant.

	<u>Cohort 4: Inflammatory disorders</u> • Patients receiving T-cell co-stimulation modulators, B-cell targeted therapies (including rituximab), tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors or JAK inhibitors • Patients who had received any immunotherapies listed above in the previous 3 months for autoimmune diseases, except in the case of rituximab treatment within the previous 6-month period, • Patients receiving or had received in the previous 6 months immunosuppressive chemotherapy • Patients receiving systemic immunosuppression for a chronic inflammatory disorder. • Cohort 4a will include participants receiving rituximab and cohort 4b will include participants receiving non-rituximab immunosuppressants
Exclusion criteria	1. Significant infection or other acute illness, including fever > 100°F (> 37.8°C) on the day prior to or day of screening 2. Prognosis of less than 6 months. 3. ECOG Performance status of >2. 4. Planned receipt of any vaccine other than the trial intervention within 30 days before and after each trial intervention (day 0 and day 28) with the exception of the seasonal influenza vaccination, and non-COVID vaccinations in the case of patients receiving a haemopoietic stem cell transplant. 5. History of serious reactions likely to be exacerbated by any component of AZD7442 and SARS-CoV-2 vaccines. 6. Anaphylactic reaction following administration of a vaccine. 7. Known history of allergy or serious reaction to any component of the trial drugs formulation. 8. Patients who are pregnant or lactating at trial entry or planning to become pregnant within 3 months after AZD7442 administration. 9. Previous hypersensitivity, clinically significant infusion-related reaction, or severe adverse reaction following administration of a mAb. 10. Any prior receipt of other mAb indicated for the prevention or treatment of SARS-CoV-2 or COVID-19 11. Clinically significant bleeding disorder (in the opinion of the investigator: e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.

	12. Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the trial, affect the ability of the participant to participate in the trial, or impair interpretation of the trial data 13. Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of trial follow-up, or concurrent participation in another interventional trial unless IMP is essential to clinical care*. 14. Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomization. 15. A history of hypersensitivity reactions including anaphylaxis and angioedema following administration of a COVID-19 vaccine 16. A history of thrombocytopenia, including immune thrombocytopenia (ITP) following administration of a COVID-19 vaccine 17. A history of Guillain-Barré Syndrome 18. Patients with acute promyelocytic leukaemia 19. Individuals with a known history of capillary leak syndrome (CLS). *Please notify the trial team (RAPID-PROTECTION@cardiff.ac.uk) of any such instances
Treatment duration	28 days
Follow-up duration	6 months
Planned trial period	9 months
Primary objectives	a. To assess the pharmacokinetics of AZD7442 administered as a single dose of 600 mg IM in immunosuppressed patients b. To assess the safety and tolerability of a single IM dose of AZD7442, followed by SARS-CoV2 vaccine booster 28 days later with reference to serious adverse events (SAEs) in highly vulnerable patients. c. To assess the SARS-CoV-2 specific humoral and cellular immune response against SARS-CoV-2 variants, when a SARS-CoV-2 vaccine is administered 28 days after AZD7442 in patients who are immune suppressed. d. To assess the effect of a SARS-CoV-2 vaccine on AZD7442 monoclonal antibody titres e. To assess neutralizing antibodies to SARS-CoV-2 using validated wild-type neutralization assay or pseudo-neutralization assays over time.
Secondary objectives	a. The incidence of participants who have a post-treatment response (negative/low at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies. b. The incidence of SARS-CoV-2 infection in trial participants. c. Sequencing of confirmed SARS-CoV2 infections to identify SARS-CoV2 variants and potential AZD7442 escape variants.

	d. To assess the behaviour of the trial participants before and after trial treatment. e. To assess if different SARS-CoV-2 vaccines will preferentially enhance humoral and/or T cell responses in immune suppressed patients receiving AZD7442. f. To assess the severity of SARS-CoV-2 infection in participants contracting COVID-19 within the duration of the trial.
Exploratory objectives	a. To investigate the mechanism of immunogenicity across disorder/disease treatment across the cohorts. b. To identify markers that predict loss/maintenance of AZD7422 titres, SARS-CoV-2 infection, response to SARS-CoV-2 vaccines, and adverse events across the cohort
Primary outcomes	a. Serum samples will be taken at Day 0, 28, 56, 112 and 180 post AZD7442 treatment b. SAE reporting throughout the trial using CTCAE V5.0 c. The function and magnitude of SARS-CoV-2 specific antibody and T cell responses measured at baseline and at additional multiple timepoints after the administration of AZD7442.
Secondary outcomes	a. SARS-CoV-2 anti NP Abs assessed over the course of the trial. b. PCR testing on days 0, 28, 56, 112 and 180 (if lateral flow test is positive for SARS-CoV-2 infection) in asymptomatic patients; plus, ad-hoc testing in symptomatic patients c. Validated behavioural questionnaire at baseline and at multiple time points over the course of the trial. d. Assessment of SARS-CoV-2 humoral and cellular responses in patients randomised to receive different SARS-CoV-2 vaccines e. Assessment of SARS-CoV-2 severity in participants contracting COVID within the duration of the trial using the WHO Clinical Progression Scale.
Tertiary/Exploratory outcomes	a. Immune data will be evaluated within and between disease and treatment cohorts. b. Immune, clinical and laboratory parameters will be assessed as predictive biomarkers for the primary and secondary trial endpoints
Investigational medicinal products	AZD7442 (EVUSHELD) Spikevax bivalent (Original/Omicron) Comirnaty bivalent (Original/Omicron BA.1)
Form	AZD7442: Solution for injection Comirnaty bivalent (Original/Omicron BA.1) and Spikevax bivalent (Original/Omicron) administered as per SmPC
Dose	AZD7442: 600mg Comirnaty bivalent (Original/Omicron BA.1) and Spikevax bivalent (Original/Omicron) administered as per SmPC
Route	AZD7442: Intramuscular injections Comirnaty bivalent (Original/Omicron BA.1) and Spikevax bivalent (Original/Omicron) administered as per SmPC

3 Trial summary & schema

3.1 Trial schema

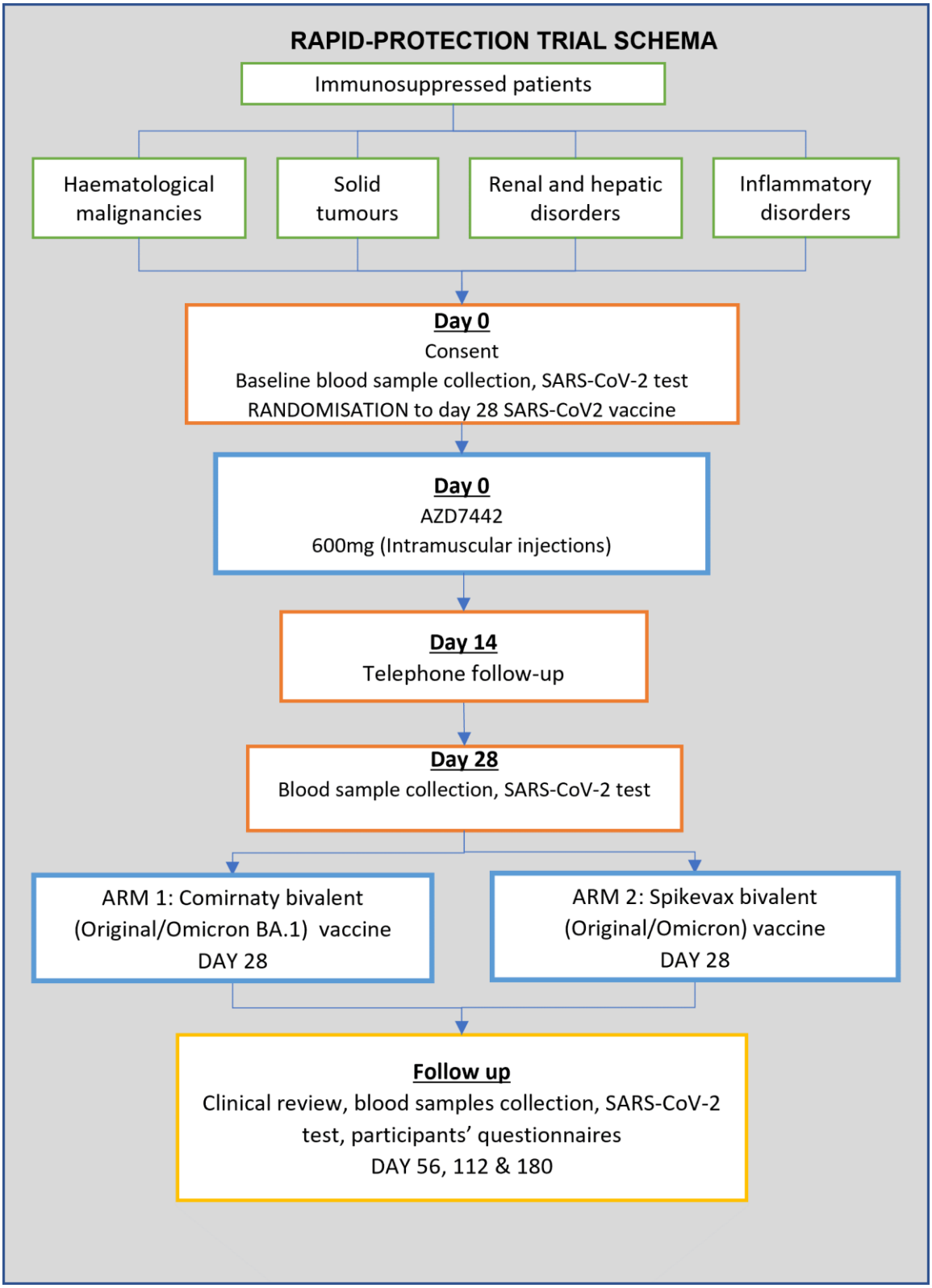

Figure 1: Flow diagram of RAPID-PROTECTION trial

3.2 Trial lay summary

Despite repeated vaccinations against COVID-19, some people with impaired immune systems caused by cancer and its treatment, inflammatory conditions, and those with organ transplants and other serious health conditions remain at very high risk of catching COVID-19 and becoming unwell.

AZD7442 (Evusheld) is a long-acting antibody treatment which has been shown in clinical trials to prevent COVID-19 infection for up to a year after a single dose. AZD7442 has been approved for use in the United States for the prevention of COVID-19 and in the UK to prevent COVID-19.

Vaccines require a healthy immune system to generate protective immunity. AZD7442 may prevent COVID-19 in people with impaired immune systems that may not have responded to repeated vaccinations against COVID-19. Unlike vaccinations, which take several doses given weeks apart to reach maximum efficacy, AZD7442 reaches effective levels within the body a few hours after a single dose.

The RAPID-PROTECTION trial will determine the levels of immune protection that AZD7442 offers patients at the very highest risk of COVID-19 infection using laboratory-based tests and whether or not this protection can be further enhanced by repeated vaccination against COVID-19. It is an adaptive platform which will allow increased recruitment in sub-groups of greatest uncertainty of effect.

All the participants in the trial will receive AZD7442 and then 28 days later a COVID-19 vaccination with either the Moderna vaccine or Pfizer/BioNTech vaccine that have been approved for use in the UK . All the participants and their trial teams will know which treatment and vaccines they have been offered in the trial. All the participants will have blood tests before, during and after each trial treatment to check the levels of AZD7442 and to examine their immune responses against COVID-19. Unless the study team specifically advise otherwise, participants will not be able to receive any of the approved NHS COVID-19 vaccines for three months after receiving their booster vaccine within the trial.

4. Background

The results from clinical trials in healthy volunteers have shown that vaccination against SARS-CoV-2 with a variety of different types of vaccines is highly effective in preventing severe disease and hospitalisation in young and old healthy adults (Polack et al, 2020, Voysey et al, 2021, Baden et al, 2021). Although phase III vaccine efficacy studies typically excluded participants from vulnerable groups such as immunocompromised individuals, emerging data have indicated that vaccination response in these individuals is both reduced and variable in its nature (Kearns, et al, 2021, Spiera et al, 2021, Prendecki et al, 2021, Boyarsky et al, 2021, Simon et al., 2021, Lesney et al, 2021, Carr et al, 2021). Approximately 60% of the population aged 65 or over within the UK suffer from chronic diseases, many of which are considered to lead to an additional risk of developing more severe SARS-

COV-2. With the rise in emerging variants and the wider circulation of the virus following the easing of restrictions, this population may require additional protection against SARS-CoV2. Here we provide an account of SARS-CoV2 infections in vulnerable patient groups, their response to vaccination and the potential role of a novel long-acting antibody (AZD7442) in protection of immunocompromised individuals against infection.

4.1 Vaccination in immunocompromised patients

Immune responses against the SARS-CoV-2 infection and vaccination are delayed and reduced in patients with immune-mediated inflammatory diseases (Simon et al, 2021) with patients with inflammatory conditions treated with rituximab at greater risk at developing more severe SARS-CoV-2 (Avouac et al, 2021). Initial results from the UK OCTAVE study have recently been published which characterised the immune response to SARS-CoV-2 vaccines in 600 patients with immune-mediated inflammatory and chronic diseases such as inflammatory arthritis, ANCA-Associated Vasculitis; inflammatory bowel disease; hepatic disease, end-stage kidney disease requiring haemodialysis without or with immunosuppression; solid organ cancers and haematological malignancies, and patients that have undergone haemopoietic stem cell transplantation (Kearns, et al, 2021).

The initial findings from OCTAVE have shown that patients with impaired immune systems have low or undetectable immune response to double vaccination against SARS-CoV-2 with 40% of the cohort studied mounting a low serological immune response after two SARS-CoV-2 vaccines when compared to healthy volunteers. Lower serological responses were seen in patients with Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (90%), inflammatory arthritis (54%), those undergoing haemodialysis (21%), haemodialysis patients receiving immunosuppressive therapy (42%), those with hepatic (liver) disease (51%), haematological malignancies (39%), solid organ cancer (17%), and haemopoietic stem cell transplantation (33%) (Kearns, et al, 2021).

The lowest serological responses to vaccination were see in patients with vasculitis treated with rituximab, an anti-CD20 monoclonal antibody which depletes B cells. These findings are similar to a study which showed that rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases (Spiera et al, 2021).

Kidney transplant patients also showed markedly reduced humoral and cellular immune responses to both the BNT162b2 and ChAdOx1 vaccines (Prendecki et al, 2021). Similarly, organ transplant recipients develop a poor anti-spike antibody response after the first dose of mRNA vaccines (Boyarsky et al, 2021). Dialysis patients demonstrated lower antibody responses than healthy controls regardless of the number of doses with haemodialysis patients particularly demonstrating poor vaccine response (Simon et al., 2021, Lesney et al, 2021, Carr et al, 2021). Several studies on vaccine response in patients with inflammatory disease have been published with varying results and limitations (Fagni et al., 2021). An initial signal of reduced vaccine immunogenicity came from a prospective cohort study of 84 patients with immune-mediated inflammatory diseases and 182 healthy participants, which

showed delayed and reduced antibody responses, with one in ten patients not having sufficient neutralising antibody responses, compared with one in 100 healthy participants (Simon et al., 2021).

Disease conditions and medications have been associated with vaccine response rates. Several studies have reported that participants taking conventional medications such as methotrexate, showed reduced rates of immunogenicity to vaccination (Al-Janabi et al, 2021, Haberman et al, 2021). Another study showed 3-fold reduction in antibody titres among patients receiving anti-metabolite therapies, and a 10-fold reduction in antibody titres among patients treated with prednisone, independently of the daily dose (Deepak et al, 2021). TNF inhibitors were shown to reduce vaccine response rates in inflammatory bowel disease compared to vedolizumab, suggesting a need to investigate patients receiving TNF blockers (Ramirez et al., 2021).

Vaccine responses in patients with cancer and other conditions are known to be reduced when compared to healthy adults. For example, vaccine responses to tetanus toxin suggest that in early cancer (high risk adjuvant setting, early and small volume recurrence (Low et al, HGT 2009, Chudley et al, CII 2012, McCann et CCR2016)) immune responses are similar in quantity and quality to healthy individuals. In contrast, in patients with end stage disease (McCann et CCR2016) or with haematological malignancies (McCann et all, 2016, McCarthy 2001, BJC, McNicholl et all 2003, Haematology Journal), a functional loss of T cell response is evident in almost 50% of patients and similar to that reported in patients who have undergone allogeneic transplants, for example of donor kidneys. Pneumococcal vaccination and annual vaccinations for seasonal influenza are routinely offered to patients with cancer before and after their cancer treatment. Studies of influenza vaccination effectiveness in patients with solid organ malignancy are around 25% compared with 8% for patients with hematologic malignancies (Blanchette et al, 2019).

Rates of seroconversion in patients are lower after SARS-CoV-2 infection in patients with haematological malignancies (82%), and in patients who received anti-CD-20 antibody therapy (59%) and stem cell transplant (60%) when compared to other groups of patients with cancer (Thakkar et al, 2021) indicating that prior SARS-CoV-2 leads to reduced immunity against re-infection against SARS-CoV-2.

In patients with solid organ and haematological cancers vaccinated with the BNT162b2 (Pfizer-BioNTech) vaccine the immune efficacy after a first vaccination in solid cancer patients is low (below 40%) and very low in haematological cancer patients (below 15%) when compared to healthy controls (>90% efficacious). Efficacy in solid cancer patients was greatly and rapidly increased by boosting at 21-days (95% within 2 weeks of boost) (Monin-Aldama et al, 2021). Another study has shown that two doses mRNA vaccination produces high seroconversion in patients with cancer and the second vaccine dose is important to boost antibody levels in these patients. Non-response to vaccine is more likely in patients with hematologic malignancy. No patients on rituximab developed antibodies even after full vaccination (Addeo et al, 2021).

In keeping with the OCTAVE trial results, anti-CD20 therapies have also been shown to blunt immune response to vaccines with timing of rituximab treatment being associated with seroconversion rates (Spiera et al, 2021, Simon et al, 2021, Bonelli et al, 2021). Patients with B-NHL treated with an anti-CD20 antibody are unlikely to achieve humoral response to SARS-COV-2 vaccines (Perry et al, 2021).

Patients with multiple myeloma have a highly variable response to SARS-CoV-2 vaccination, with no detectable responses to SARS-CoV-2 vaccination in some cases (Van Oekelen et al, 2021). In patients with chronic lymphocytic leukaemia, antibody responses to BNT162b2 mRNA SARS-CoV-2 vaccine are markedly impaired and affected by disease activity and treatment such as Bruton's tyrosine kinase inhibitors or venetoclax ± anti-CD20 antibody (Herishanu et al, 2021).

The growing body of research suggests that immunocompromised patients may remain at higher early risk of SARS-CoV-2 infection despite vaccination with emerging data of SARS-CoV-2 related deaths supporting correlation between absence of detectable immunological response and efficacy in some of the above population groups (Caillard et al, 2021, Tau et al, 2021). Given the potentially increased exposure of these patient groups to infection, for example additional hospital visits for treatment such as chemotherapy and dialysis, alternative treatments and monitoring are required to protect these patient groups.

4.2 Multiple vaccine doses

Immunisation against SARS-CoV-2 for the severely immunocompromised comprises three primary doses followed by a number of booster vaccines. The number of recommended booster doses has changed as the pandemic evolved (depending on time since the third dose, proximity to autumn, etc). It is anticipated that advice on boosters will continue to evolve. For the purposes of this trial, severely immunocompromised participants will be considered to be "fully" immunised if they have received all three primary doses, regardless of the number (if any) of booster doses received. The effectiveness of booster doses is significantly reduced in certain groups of patients, such as those with solid organ transplants (Werbel et al, 2021), when compared with healthy volunteers (Flaxman et al, 2021). Furthermore, there are relatively few data on the effectiveness of a third or a fourth SARS-CoV-2 vaccine in patients that are extremely vulnerable to SARS-CoV-2 infection. Official UK government advice regarding vaccination in the immunocompromised can be found here: https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/ and https://www.gov.uk/government/news/jcvi-issues-updated-advice-on-covid-19-booster-vaccination.

Despite widespread global vaccination, SARS-COV-2 has become an endemic infection, requiring repeated vaccinations for higher risk patients in a manner similar to seasonal influenza against current dominant strains of SARS-CoV-2. The results from OCTAVE and other published studies indicate that substantial proportions of patients with diminished immune response capacity do not respond to SARS-CoV-2 vaccines and remain at risk of SARS-CoV-2 infection despite vaccination. This means that, until better protection against SARS-CoV-2 can be provided to this group of patients, they will increasingly have to take measures to socially distance themselves from healthy society which will have a negative effect on their quality of life.

New clinically validated therapeutic approaches, are therefore urgently needed to protect immunosuppressed patients from SARS-CoV-2 infection.

4.3 AZD7442 for the prevention of SARS-CoV-2 in immunosuppressed patients

Potently neutralizing antibodies against SARS-CoV-2, such as AZD7442, have been shown in pre-clinical models to protect against SARS-CoV-2 infection (Zost el al, 2020) and reduce the incidence of symptomatic SARS-CoV-2 in patients (PROVENT trial: ClinicalTrials.gov Identifier: NCT04625725). AZD7442 is a combination of two long-acting antibodies (LAABs) – (AZD8895/ COV2-2196) and cilgavimab (AZD1061) which were derived from B-cells donated by convalescent patients after SARS-CoV-2 virus.

4.4 Summary of Nonclinical Pharmacology

The AZD7442 human monoclonal antibodies bind to distinct sites on the SARS-CoV-2 spike protein (Dong et al, 2021). The SARS-CoV-2 spike protein contains the receptor-binding domain (RBD), which enables the SARS-CoV-2 virus to bind to receptors on human cells. By targeting the RBD region of the virus's spike protein, AZD7442 blocks the virus's attachment to human cells to prevent infection. Both AZD8895 and AZD1061 bind the RBD with nanomolar affinity and are individually capable of sterically blocking the virus from engaging its cellular receptor, ACE2. This binding translates to potent neutralization of SARS-CoV-2 infection by AZD7442 in vitro, with an IC50 value of approximately 10 ng/Ml.

AZD7442 has been optimised for half-life extension and reduced Fc receptor and complement C1q binding (Griffin et al, 2017) to minimise the risk of antibody-dependent enhancement of SARS-CoV-2 infection as the binding of Fc receptors to virus-specific antibodies can lead to antibody-dependent enhancement of infection (Erp et al, 2019). Additional modifications induce half-life extensions significantly increasing the time of AZD7442's action when compared to conventional antibodies (Domachowske et al, 2018, Robbie et al, 2013, Yu et al, 2017) and may offer up to 12 months of protection from SARS-CoV-2 infection following a single intramuscular injection of AZD7442.

SARS-CoV-2 is an RNA virus capable of rapid mutation, which can lead to amino acid changes in the spike protein that impact the efficacy of vaccines and mAb therapies. A combination mAb approach that includes two complementary mAbs, like AZD7442, is expected to retain efficacy even if a virus variant emerges with mutations that confer resistance to one of the mAbs. In vitro studies confirm that viruses with reduced susceptibility to AZD8895 or AZD1061 individually remain susceptible to the combination.

The combination also demonstrated synergy in in-vitro neutralization assays Importantly, in-vitro potency evaluations of SARS-CoV-2 and/or spike-pseudotyped virus demonstrates that AZD7442 neutralizes: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) emergent SARS-CoV-2 variants of concern (Loo et al 2021, Wang et al 2021a, Wang et al 2021b, Lusvarghi et al 2021, Liu et al 2021, Dejnirattisai et al 2021, Zhou et al 2021). Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1) and Lambda (C.37) SARS-CoV-2 variants of interest (Liu et al 2021, Lusvarghi et al 2021, Chen et al 2020a, Dong et al 2021). Epsilon (B.1.427 / B.1.429), Zeta (P.2), R.1, and B.1.1.519 former variants of interest and/or variant alerts for further monitoring (Liu et al 2021, Lusvarghi et al 2021, Chen et al 2020a, Dong et al 2021). In-vitro neutralisation studies have shown that AZD7442 can neutralise the Omicron (B.1.1.529) SARS-CoV-2 Variant of Concern (Dejnirattisai et al, 2021).

4.5 Summary of Clinical Data

One Phase I FTIH study (D8850C00001) and 3 Phase III studies (D8850C00002 [PROVENT; pre-exposure prophylaxis], D8850C00003 [STORM CHASER; post-exposure prophylaxis], and D8851C00001 [TACKLE; treatment of COVID-19]) in adults are ongoing with AZD7442. In addition, participation in 3 externally-sponsored platform studies (ACTIV-2 and ACTIV-3 [sponsored by NIAID] and DisCoVeRy [sponsored by Inserm]) are ongoing with AZD7442.

AZD7442 has been found to prevent symptomatic SARS-CoV-2 infection in the PROVENT study. The PROVENT study is phase III double-blind placebo-controlled study of AZD7442 for pre-exposure prophylaxis of SARS-CoV-2 in adults. In the PROVENT study a total of 5197 participants were randomized and dosed in a 2:1 ratio to receive a single dose (x 2 IM injections) of either AZD7442 300 mg (N = 3460) given as two sequential IM injections of AZD8895 and AZD1061 (one in each gluteal region), or corresponding placebo on Day 1. Randomization was stratified into two cohorts: Cohort 1: Adults ≥ 60 years of age. All such participants were considered as being at increased risk for inadequate response to active immunization on the basis of age (presumed immunosenescence). Cohort 1 was capped, not to exceed 80% of total participants randomized. Within this cohort, randomization was stratified by residence in a long-term care facility or not. Cohort 2: Adults < 60 years of age. Cohort 2 was capped, not to exceed 80% of total participants randomized. Within this cohort, randomization was stratified by risk of exposure to infection with SARS-CoV-2.

As of the primary analysis data cut-off of 05 May 2021, randomization was complete, 5254 participants (3500 AZD7442 and 1754 placebo) had been randomized, 5109 (97.2%) (3409 [97.4%] AZD7442 and 1700 [96.9%] placebo) were ongoing in the study, and 145 (2.8%) participants (91 [2.6%] AZD7442 and 54 [3.1%] placebo) had discontinued the study. The mean age of participants was 53.5 years. Most participants were White (3794 [73.0%]), 899 (17.3%) were Black or African American, and 170 (3.3%) were Asian. A slightly higher proportion of participants were male (53.9%) than female (46.1%).

The primary outcome measures of PROVENT were the incidence of the first case of SARS CoV-2 RT PCR positive symptomatic illness [Time Frame: Day 183] and to estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-COV-2 prior to Day 183, and to assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo.

Positive high-level results from PROVENT showed that AZD7442, reduced the risk of developing symptomatic SARS-CoV-2 by 77% (95% confidence interval (CI): 46, 90), when compared to placebo. There were no cases of severe SARS-CoV-2 or SARS-CoV-2-related deaths in those treated with AZD7442. In the placebo arm, there were three cases of severe SARS-CoV-2, which included two deaths. AZD7442 was well tolerated and preliminary analyses show adverse events were similar between the placebo and AZD7442 groups (https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html).

More than 75% of participants had co-morbidities, which include conditions that have been reported to cause a reduced immune response to vaccination. Approximately 43% of participants were 60 years and over. In addition, more than 75% had baseline co-morbidities and other characteristics that are associated with an increased risk for severe SARS-CoV-2 should they become infected, including those with immunosuppressive disease or taking immunosuppressive medications, diabetes, severe obesity

or cardiac disease, chronic obstructive pulmonary disease, chronic kidney and chronic liver disease. The results from PROVENT show that AZD7442 can prevent SARS-CoV-2 in symptomatic high-risk populations. However, within the PROVENT study, there were limited numbers of patients at the highest risk of developing SARS-CoV-2, and all of the study participants were unvaccinated against SARS-CoV-2.

4.6 Observed Clinical Safety with AZD7442

Primary analysis of safety data from the Phase I Study D8850C00001 (data cut-off date 06 June 2021), for Cohort 1a (AZD7442 300 mg or placebo IM), Cohort 1b (AZD7442 300 mg or placebo IV), Cohort 2 (AZD7442 1000 mg or placebo IV), Cohort 3 (AZD7442 3000 mg or placebo IV), and Cohort 4 (AZD7442 3000 mg co-administered, or placebo IV) in healthy adult volunteers:

- There were no deaths, SAEs, or discontinuation of IP due to AEs in any subject.
- 3 (25.0%) participants in Cohort 1a had reported 6 AEs: palpitations, vessel puncture site pain, nasopharyngitis, urinary tract infection, back pain, and paresthesia. Paresthesia was considered causally related to IP by the Investigator.
- 5 (41.7%) participants in Cohort 1b had reported 14 AEs: headache (2 participants), abdominal pain (2 participants), abdominal distension (2 participants), lymphadenitis, diarrhoea, nausea, increased malaise, pain in extremity, urinary tract infection and tremor (1 subject each). Headache, tremor, and lymphadenitis were considered causally related to IP by the Investigator
- 7 (58.3%) participants in Cohort 2 had reported 13 AEs: headache (2 participants), toothache (2 events in 1 subject and 1 event in another subject), tooth repair, abdominal discomfort, back pain, diarrhoea, fatigue, myalgia, application site irritation and dysmenorrhea (1 subject each). Fatigue and myalgia were considered causally related to IP by the Investigator.
- 7 (58.3%) participants in Cohort 3 had reported 13 AEs: headache (3 participants), back pain (2 events in 1 subject), nasal congestion (2 participants), oral herpes, arthralgia, rhinorrhoea, heavy menstrual bleeding, myalgia, and oropharyngeal pain (1 subject each). Headache (2 participants) and arthralgia were considered causally related to IP by the Investigator.
- 7 (58.3%) participants in Cohort 4 had reported 10 AEs: fatigue (2 participants), headache (2 participants), back pain, dizziness, musculoskeletal discomfort, hypoaesthesia, injury, and oropharyngeal pain (1 subject each). Headache and fatigue (1 subject each) were considered causally related to IP by the Investigator.
- All AEs reported were mild in intensity, with the exception of the following events of moderate intensity: urinary tract infection (1 subject) in Cohort 1a; headache, malaise (1 subject each) and urinary tract infection (1 subject) in Cohort 1b; dysmenorrhea and headache (1 subject each) and toothache (2 participants) in Cohort 2; headache, back pain, and arthralgia (1 subject each) in Cohort 3; and back pain (1 subject) in Cohort 4.
- There were no haematology, clinical chemistry, or vital signs findings of concern in any subject.

In addition, by Day 211, no participants in the study tested positive for ADA to either AZD8895 or AZD1061. Since ADA-positive to AZD7442 is defined as having a positive result to AZD8895 and/or AZD1061, no participants tested positive for ADA to AZD7442. Thus, both ADA prevalence (percentage

of ADA-positive participants in the study) and ADA incidence (percentage of treatment-emergent ADA-positive participants in the study) were 0%. The serum AZD8895 and AZD1061 concentrations observed in the Phase I study support that the PK of the 2 antibodies are similar. The half-life of AZD7442 is estimated to be ~ 90 days which will allow for long-term protection. Overall, the Cmax and AUC increased linearly with increasing IV dose. Administering AZD8895 and AZD1061 separately or together did not alter the PK of the mAbs as indicated by the overlapping serum drug concentration-time curves. In addition, key exposure PK parameters such as AUC and Cmax for AZD8895 and AZD1061 were similar between the 2 dosing regimens.

All 50 participants receiving AZD7442 exhibited > 4-fold increases in neutralizing antibody titer at 7 days after treatment; all 40 patients with available data at 30 days after treatment maintained this increase out to Day 211. Participants in the 300-mg cohorts further maintained this 4-fold increase in nAb titre out to Day 271 post-treatment. These results are consistent with the expected pharmacodynamic activity of AZD7442 and demonstrate a dose dependent increase in nAb, with the 3000 mg dose cohorts showing approximately 3.5, 16.1, and 29.7 greater fold changes than the 1000 mg, 300 mg IV, and 300 mg IM, respectively, after 7 days of treatment; 2.7, 9.0, and 13.0 greater fold changes after 150 days of treatment; and 4.3, 10.4, and 13.7 greater fold changes after 210 days of treatment. Across all doses and timepoints evaluated, the levels of nAbs exceeded the mean nAb titres measured in the same assay in 28 individual convalescent plasma samples.

Specifically, participants treated with 300 mg of AZD7442, either IM or IV, exhibit approximately 10 to 15-fold higher GMT at Day 91, 6 to 8-fold higher GMT at Day 151, and 2 to 3-fold higher GMT at Day 271 compared to the GMT measured in convalescent plasma from SARS-COV-2 patients (GMT = 50; n = 28). No safety signals were observed in this healthy adult population. These results demonstrated an acceptable safety profile for AZD7442, including no observed infusion-related reactions, injection site reactions, or hypersensitivity reactions. Overall, the results support the use of AZD7442 in further clinical studies.

4.6.1 Phase III Study D8850C00002 (PROVENT)

The DCO date for the primary analysis was defined as the date the 24th primary endpoint event had been confirmed across the active and placebo groups or 30% of study participants have become unblinded, whichever occurred earlier. The DCO of the primary analysis was 05 May 2021. High-level results from the PROVENT Phase III pre-exposure prophylaxis study showed that AZD7442 achieved a statistically significant reduction in the incidence of symptomatic SARS-CoV-2, the study's primary endpoint. Furthermore, AZD7442, reduced the risk of developing symptomatic SARS-CoV-2 by 77% (95% CI: 46, 90), compared to placebo. The study accrued 25 cases of symptomatic SARS-CoV-2 at the primary analysis. As of the primary analysis data cut-off of 05 May 2021, AZD7442 was well tolerated and preliminary analyses showed AEs were balanced between the placebo and AZD7442 groups. There were no cases of severe SARS-CoV-2 or SARS-CoV-2 -related deaths in those treated with AZD7442. In the placebo arm, there were 3 cases of severe COVID-19, which included 2 deaths.

Primary analysis of safety data from the Phase III Study D8850C00002 (data cut-off date 05 May 2021):

- 1221 (35.3%) participants in the AZD7442 300 mg IM group and 593 (34.2%) participants in the placebo group had reported AEs. A total of 73 (1.4%) participants had reported SAEs (50 [1.4%] in the AZD7442 300mg IM group and 23 [1.3%] in the placebo group).
- The proportions of participants reporting at least one AE were similar in both groups (AZD7442 1221 [35.3%] compared to placebo 593 [34.2%]). Individual AE preferred terms were balanced across the treatment groups.
- At the time of primary analysis, 130 (2.5%) participants had reported an AESI (93 [2.7%] in the AZD7442 group and 37 [2.1%] in the placebo group) Anaphylaxis: 1 (0.0%) participant in the AZD7442 group and 0 in the placebo group, immune complex disease: 1 (0.0%) participant in the AZD7442 group and 0 in the placebo group, Injection site reactions: 118 (2.3%) participants (82 [2.4%] in the AZD7442 group and 36 [2.1%] in the placebo group). Other: 11 (0.2%) participants (9 [0.3%] in the AZD7442 group and 2 [0.1%] in the placebo group).
- 1 participant had an AE leading to discontinuation from the study.
- 8 participants had AEs with an outcome of death (4 [0.1%] in the AZD7442 300 mg IM group and 4 [0.2%] in the placebo group). Of these, 0 in the AZD7442 group and 2 (0.1%) in the placebo group were adjudicated to be related to SARS-COV-29. Preferred terms reported for deaths were: AZD7442 group: myocardial infarction (n = 1), overdose (n = 2), and renal failure (n = 1) Placebo group: SARS-COV-2 (n = 1), overdose (n = 2), acute respiratory distress syndrome (n = 1)

4.6.2 Phase III Study D8850C00003 (STORM CHASER)

The DCO date for the primary analysis was defined as 30 days after the 25th primary efficacy event had been reported across the active and placebo groups and all additional primary endpoint events collected during this period were included in the primary analysis. The DCO of the primary analysis was 07 April 2021. With 23 cases of symptomatic SARS-CoV-2 accrued in the AZD7442 arm (23/749) and 17 cases accrued in the placebo arm (17/372), all participants had a negative SARS-CoV-2 antibody test on the day of dosing to exclude prior infection, and a nasopharyngeal swab was also collected and subsequently analysed for SARS-CoV-2 by RT-PCR to detect virus. In the overall study population, AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 by 33% (95% CI: -26, 65) compared to placebo, which was not statistically significant.

However, in a pre-planned analysis of SARS-CoV-2 PCR positive (detectable virus) and PCR negative (no detectable virus) participants, AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 by 73% (95% CI: 27, 90) compared with placebo, in participants who were PCR negative at time of dosing. In a post-hoc analysis, in participants who were PCR negative at baseline, AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 by 92% (95% CI: 32, 99) versus placebo more than 7 days following dosing, and by 51% (95% CI: -71, 86) up to 7 days following dosing. As of the primary analysis data cut-off of 07 April 2021, there were no AEs leading to deaths and no AEs resulting in

discontinuation of IMP or discontinuation from the study. Preliminary analyses show similar adverse events in the placebo and treatment arms. AZD7442 was well tolerated in the study.

Primary analysis of safety data from the Phase III Study D8850C00003 (data cut-off date 07 April 2021):

- A lower proportion of participants in the AZD7442 (162 [21.6%]) group experienced AEs compared to placebo (111 [29.8%]).
- The majority of participants with AEs had events that were mild or moderate in severity. Overall, 13 (1.2%) participants (7 [0.9%] participants in the AZD7442 group and 6 [1.6%] participants in the placebo group) had events of severe intensity, and 1 (0.1%) participant in the AZD7442 group had events of potentially life-threatening intensity (overdose and suicide attempt).
- A total of 8 participants had reported SAEs (5 [0.7%] in the AZD7442 300 mg IM group and 3 [0.8%] in the placebo group).
- At the time of primary analysis, 9 (0.8%) participants had reported an AESI (4 [0.5%] in the AZD7442 group and 5 [1.3%] in the placebo group). None of the AESI included anaphylaxis or serious hypersensitivity reactions, and none of the AESIs were considered SAEs.
- In the AZD7442 group, injection site reactions included 3 (0.4%) participants with injection site pain and 1 (0.1%) participant with pruritus. In the placebo group, injection site reactions included 1 (0.3%) participant with injection site pain, 2 (0.5%) with injection site pruritus, and 1 (0.3%) with injection site reaction. For AESI 'other' 1 (0.3%) participant also reported pruritus.
- There were no AEs leading to deaths and no AEs resulting in discontinuation of IMP or discontinuation from the study.
- There were no clinically significant changes in vital signs or clinical chemistry, haematology and coagulation.

4.6.3 Rationale for AZD7442 dose

In February 2022, in response to concerns regarding effectiveness of the AZD7442 against the Omicron variant, the FDA revised the EUA to increase the initial dose of AZD7442 from 300mg (150mg tixagevimab (AZD8895) and 150mg cilgavimab (AZD1061)) to 600mg (300mg tixagevimab (AZD8895) and 300mg cilgavimab (AZD1061)). The recommendations for dosing were based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data (US Food and Drug Administration FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™).

Evaluation of AZD7442 on the Omicron BA.2, BA.4, and BA.5 variants has shown that AZD7442 retained neutralisation activity, with modelling assessments indicating that a higher dose of AZD7442 would be more effective at neutralising these variants (VanBlargan et al., 2022, Dejnirattisai et al., 2022, Tuekprakhon et al., 2022, Vector Engineering Lab et al., 2022, National Institutes of Health).

Emerging real-world evidence in immunocompromised patients who received 600mg during the Omicron wave and safety and efficacy data from the TACKLE study and ongoing PROVENT Phase III trial supports the use of 600mg of Evusheld (Montgomery et al., 2022, Jurdi et al., 2022, Young-Xu et al., 2022).

The safety profile of AZD7442 given at 600mg is generally well tolerated and consistent with the 300mg IM dose (Montgomery et al., 2022, US Food and Drug Administration FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™).

Given the FDA recommendations and the similar safety profile between 300mg and 600mg dose, the 600mg of AZD7442 was selected for use in this study.

4.6.4 The rationale for combining AZD7442 and an additional vaccine booster

No data are currently available to characterize the effects of giving AZD7442 to a person who has received a course of vaccination against SARS-CoV-2. Most such individuals will have developed active immunity against the virus from having received the vaccine.

The majority of SARS-CoV-2 vaccinations performed in the UK used the mRNA vaccine BNT162b2 (Pfizer/BioNTech) or chimpanzee adenovirus vector vaccine Vaxzevria (Astra Zeneca). Multiple studies have now shown that the heterologous prime boost schedules are highly effective in preventing severe SARS-CoV-2 disease with no safety concerns (Liu et al., 2021, Gram et al., 2021). Added benefit in a mixed vaccination schedule in comparison to non-mixed schedules have been reported. Those on a mixed vaccination schedule were 68% less likely to develop a symptomatic infection, whereas the 430,000 people who received two doses of the AstraZeneca vaccine were 50% less likely to do so (Nordström et al., 2021).

A French study showed that health-care workers who received a combination of AstraZeneca and Pfizer vaccines had half the rate of infection when compared to those who received two doses of the Pfizer vaccine (Pozzetto et al., 2021). A German study also recently showed that immunosuppressed individuals mount a strong immune response to mixed regimens (Schmidt et al., 2021) with the suggestion that mixing doses could protect immunocompromised individuals more than do the standard regimens.

Although both booster vaccines and AZD7442 prevent SARS-CoV-2 infection and reduce the risk of life-threatening infection, they have different mechanisms of action which are complementary, and potentially immunologically synergistic. Furthermore, although the response of immunocompromised patients to SARS-CoV-2 vaccination are lower than heathy controls, immunocompromised patients will still be recommended to receive SARS-CoV-2 vaccination, even if treated with AZD7442, to maximise their protection against SARS-CoV-2.

Importantly, AZD7442 reaches therapeutic levels within 4 hours of IM injection, whereas SARS-CoV2 vaccines takes up to two doses given 12 weeks apart to induce maximum protection against the infection. Therefore, giving AZD7442 could potentially induce rapid protection in patients undergoing procedures like haematological stem cell transplantation, whilst their adaptive immunity recovers after their transplantation to allow them to respond to vaccination.

The PROVENT study recruited patients that were not vaccinated against SARS-CoV-2, and since PROVENT completed enrolment, SARS-CoV-2 vaccinations have been widely administered around the world. Although it is known that booster doses of SARS-CoV-2 vaccines enhance SARS-CoV-2 immunity in healthy volunteers (Flaxman et al, 2021), it is not known if the same applies to patients with impaired immunity that have had previous SARS-CoV-2 vaccinations/boosters (https://www.gov.uk/government/news/jcvi-issues-interim-advice-on-covid-19-booster-vaccination).

At the present time, there are no clinical studies which have evaluated the safety or immunogenicity of AZD7442 given in combination with SARS-CoV-2 vaccination boosters. PROVENT only included a small subset of patients with highly immunosuppressive conditions.

Therefore, additional clinical studies are required to further delineate the immunological effects of giving AZD7442 to patients with immunosuppressive conditions either alone or followed by vaccination as a standard of care treatment. These studies will also confirm that the protective effect of AZD7442 is maintained against SARS-CoV-2 over the 12-month period between injection and whether booster vaccinations further enhance immune protection through enhanced humoral and cellular responses against SARS-CoV-2 after previous vaccination against SARS-CoV-2 and whether the combination is safe in highly immunosuppressed patients.

4.7 Rationale for current trial/Justification of Treatment Options

This is an adaptive trial to assess the safety and immunogenicity of the AZD7442 and SARS-CoV-2 vaccines in patients that are highly immunocompromised against SARS-CoV-2 infection. Adaptation will occur to drive continued recruitment in particular sub-groups to distinguish between the patients who benefit from AZD7442 and those who do not. Improvement in immune responses seen 28 days after administration of AZD7442 will be compared to healthy volunteers in other trials such as the PROVENT clinical trial, and other trials of AZD7442 and SARS-CoV-2 vaccines. Where there is increased variability in the response than the healthy population, analysis will be divided into subgroups to plan extending recruitment.

All participants who consent will be randomised to receive one of the UK approved vaccines currently in deployment to assess the impact of the mAb on response to the vaccine.

4.7.1 Hypotheses to be tested

1) That treatment with AZD7442 in combination with a SARS-CoV-2 vaccine is safe and well tolerated,

2) That vaccination with a SARS-CoV-2 vaccine does not reduce AZD7442 titres in humans and

3) That AZD7442 in combination with a SARS-CoV-2 vaccine enhances immune responses to SARS-CoV-2.

5 Trial objectives/endpoints and outcome measures

We propose to test the following objectives:

Table 1: Objectives and outcome measures

	Objectives	**Outcome measures**
Co-Primary	To assess the pharmacokinetics of AZD7442 administered as a single dose of 600 mg IM in immunosuppressed patients	Serum samples will be taken at Day 0 (Predose AZD7442), and days 28, 112 and 180 post AZD7442 treatment and samples shipped to an AstraZeneca approved laboratory for Pharmacokinetics (PK) analysis. Samples collected for analyses of AZD7442 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the trial. PK results from the trial will be compared to results from other phase III studies with AZD7442 such as PROVENT.
	To assess the safety and tolerability of a single IM dose of AZD7442, followed by SARS-CoV2 vaccine booster 28 days later with reference to serious adverse events (SAEs) in highly vulnerable patients.	SAE reporting throughout the trial using CTCAE V5.0
	To assess the SARS-CoV-2 specific humoral and cellular immune response against SARS-CoV-2 variants, when a SARS-CoV-2 vaccine is administered 28 days after AZD7442 in patients who are immune suppressed.	The function and magnitude of SARS-CoV-2 specific antibody and T cell responses will be measured at baseline and at additional multiple timepoints after the administration of AZD7442. Assays will quantify the amount of serum antibodies to 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. Ab function, including viral neutralisation will be assessed.

		The magnitude and function of SARS-CoV-2 specific T cell responses following the booster vaccination will use assays that give insight into T cell function. Laboratories will measure neutralizing antibodies to SARS-CoV-2 using validated wild-type neutralization assay or pseudo-neutralization assays.
	To assess the effect of a SARS-CoV-2 vaccine on AZD744 monoclonal antibody titres.	Serum samples will be taken at Day 0 (Predose AZD7442), and days 28, 56, 112 and 180 post AZD7442 treatment and vaccination and samples shipped to an AstraZeneca approved laboratory for quantification of the AZD744 monoclonal Abs generated by therapeutic vaccination, natural infection and vaccinations.
Secondary	The incidence of participants who have a post-treatment response (negative/low at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.	Measurement of SARS-CoV-2 anti NP Abs assessed over the course of the study.
	The incidence of SARS-CoV-2 infection in trial participants.	Self-reported throughout the study duration and assessed at follow up visits. Lateral flow testing for SARS-CoV-2 infection in a subset of asymptomatic participants on days 0, 28, 56, 112 and 180. If the lateral flow test is positive for SARS-CoV-2, a nasal PCR swab will be taken to be sent for PCR testing. Ad-hoc PCR testing in all symptomatic patients. Measurement of SARS-CoV-2 Anti-NP IgG titres
	Sequencing of confirmed SARS-CoV-2 infections to identify SARS-CoV-2 variant and potential AZD7442 escape variants.	Lateral flow testing for SARS-CoV-2 infection in a subset of asymptomatic participants on days 0, 28, 56, 112 and 180. If the lateral flow test is positive for SARS-CoV-2, a nasal PCR swab will be taken to be sent for PCR testing. Ad-hoc PCR testing in all symptomatic patients.

	To assess the behaviour of the trial participants before and after trial treatment.	Validated behavioural questionnaire completed by the participants at baseline and at multiple time points over the course of the trial.
	To assess if different SARS-CoV-2 vaccines will preferentially enhance humoral and/or T cell responses in immune suppressed patients receiving AZD7442	Assessment of SARS-CoV-2 humoral and cellular responses in patients randomised to receive different SARS-CoV-2 vaccines
	To assess the severity of SARS-CoV-2 infection contracting COVID-19 within the duration of the trial.	Assessment of SARS-CoV-2 severity in participants contracting COVID-19 within the duration of the trial using the WHO Clinical Progression Scale.
Exploratory	To investigate the mechanism of immunogenicity across disorder/disease treatment across the cohorts.	Immune data will be evaluated within and between disease and treatment cohorts.
	To identify markers that predict loss/maintenance of AZD7422 titres, response to SARS-CoV-2 vaccines, SARS-CoV-2 infection and adverse events across the cohort.	Immune, clinical and laboratory parameters will be assessed as predictive biomarkers for the primary and secondary trial endpoints.

6 Trial design and setting

The trial is a multicentre, open-label, phase II trial with a randomised comparison of vaccine booster type at 28 days following AZD7442 treatment. Up to 350 patients will be recruited and treated at NHS sites including those already participating in the studies of candidate SARS-CoV-2 vaccines and other interested sites in the UK. Participants will be recruited from groups known to be highly vulnerable to SARS-CoV-2 and therefore likely to benefit from AZD7442 as defined by those recommended as high priority by the Joint Committee on Vaccination and Immunisation (JCVI) (see appendix 1). Patients will be stratified by cohort into 4 groups: Haematological malignancies, Solid tumours, Renal and Hepatic disorders and inflammatory disorders.

All participants will receive AZD7442 treatment followed by vaccination with SARS-CoV2 vaccine booster 28 days later. Immunogenic response will be measured at baseline, throughout treatment and at follow up. The design of the prospective cohort will be initially observational with all participants receiving AZD7442 treatment followed by randomisation to a vaccination with SARS-CoV-2 vaccine booster. The cohorts will be sub divided into subgroups for comparison to healthy volunteers.

Participants will be subdivided into 4 subgroups (see figure 2); up to 120 of these patients enrolled at Oxford University Hospitals NHS site will have additional translational bloods for the additional immunological studies described within the protocol. The Oxford site will decide in conjunction with

the trial management team on which patients from each cohort at the Oxford site will have standard study bloods or translational bloods tests.

Where subjects have conditions that allow entry into more than one cohort of the study then the subject will be allocated into the cohort for the condition that they have had the longest, should that cohort be full, then the subject will be allowed to enter the other cohort for their other condition.

Cohort 1: Haematological malignancies (anticipated 70 participants)

Patients with haematological malignancies and haemopoietic stem cell transplantation will be subdivided into patients receiving active therapy with immunosuppressive or immunomodulating agents (Cohort 1a) and patients receiving aggressive therapy expected to cause temporary ablation of immune function (Cohort 1b).

Cohort 2: Solid tumours (anticipated 70 participants)

The cancer cohorts will be subdivided into the following subgroups for comparison to healthy volunteers:

- Early cancer on systemic treatment (Cohort 2a)
- Advanced cancer on systemic treatment (Cohort 2b)

Cohort 3: Renal and Hepatic disorders (anticipated 70 participants)

Patients with renal (Cohort 3a) and hepatic disorders (Cohort 3b) will be divided into those receiving immunosuppression as part of their treatment, patients with advanced disease for example kidney disease on dialysis, or liver cirrhosis and liver and renal transplantation.

Cohort 4: inflammatory disorders (anticipated 70 participants)

Patients' inflammatory disorders will be divided into those receiving rituximab or not and those receiving other forms of immunosuppressants. Cohort 4a will include participants receiving rituximab and cohort 4b will include participants receiving non-rituximab immunosuppressants.

Each treatment group will then be compared to age-matched healthy volunteers from the mid-2021 phase 1 and 3 trials of AZD7442 and SARS-CoV-2 vaccine booster for both point estimator and variance, and across all patient cohorts.

This will be an adaptive trial that will extend recruitment in any sub-group where more information is required in order to come to a reliable estimator. The immunological assessments will be analysed to allow cohorts to be expanded in case of poor immunogenicity to SARS-CoV-2 or closed if good immunogenicity against SARS-CoV-2 is seen. Recruitment of patients from each group will be limited to ensure the trial captures a representative group of patients from all major immunosuppressive groups most at risk of SARS-CoV-2 mortality. The group sizes will be calculated based on the expected heterogeneity of the group and the degree of variability in the general population.

This may include subdividing groups by disease type in order to gain more homogenous responses. The decision making for these adaptations will be undertaken using a Bayesian partitioning approach adapted from Nugent et al, 2019, details currently under development. The anticipated 70 participants per group is based on expected attrition.

Allowing for an assumed attrition rate of 20% recruitment of 350 participants is anticipated to take 3 months across 4 to 6 sites. Participants will continue on follow up for 6 months.

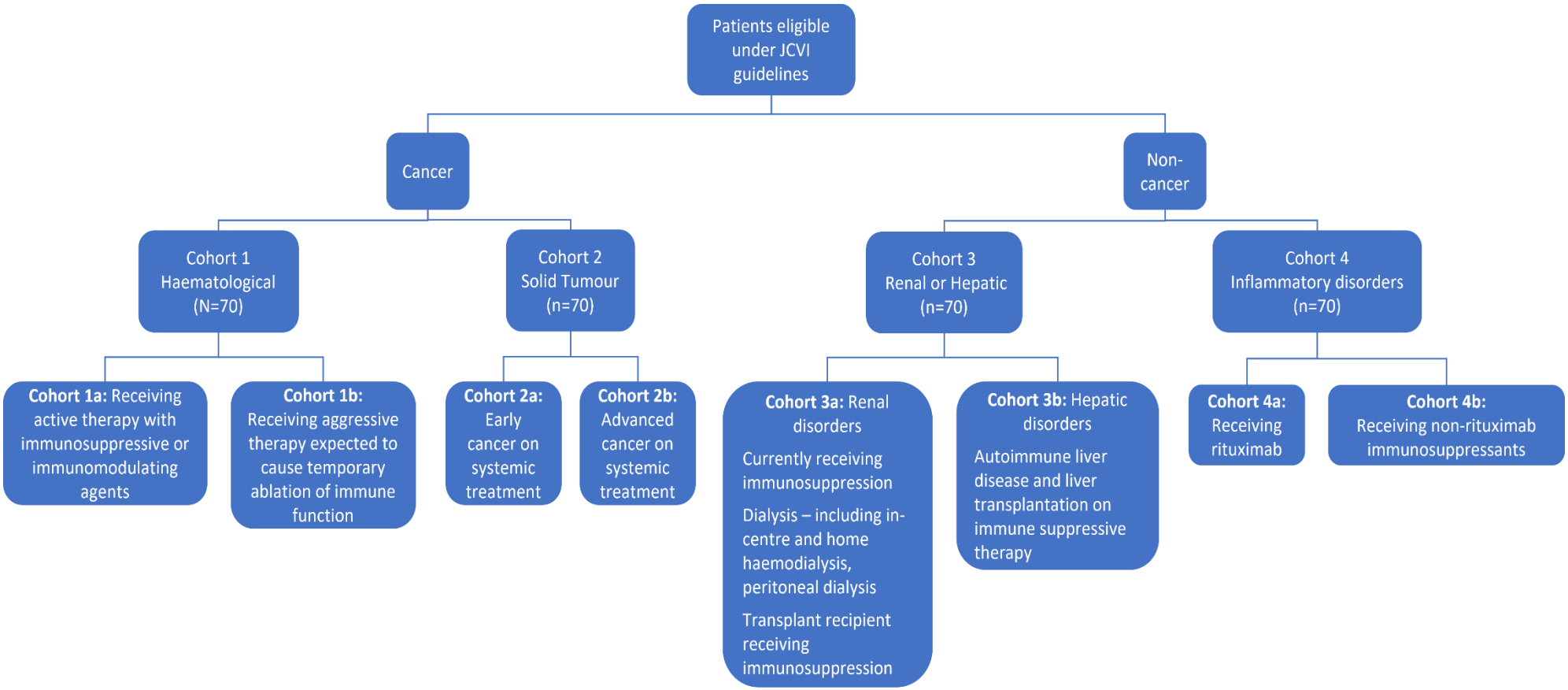

Figure 2: Cohorts and further sub-grouping of immunocompromised participants

Remote data capture will be used (see section 17.1). Samples will be collected both for trial end points and for future research (see section 12 for more information). Participants will be asked to complete questionnaires at the relevant timepoints.

6.1 Risk assessment

6.1.1 Benefit/Risk Assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

1. The known and potential risks and benefits to human participants
2. How high the risk is compared to normal standard practice
3. How the risk will be minimised/managed

6.1.2 Risk assessment of AZD7442

The two monoclonal antibodies that make up AZD7442 both target SARS-CoV-2 spike protein for neutralization of the virus and do not have a human target. As such, the risks associated with AZD7442 are akin to risks associated with the administration of any immunoglobulin with no risk associated with mechanism of action.

As with other immunoglobulins, risks include but are not limited to, anaphylaxis and other serious hypersensitivity reactions including immune complex disease. Other risks include injection site reactions, and Antibody-dependent enhancement (ADE) disease, the latter of which is a theoretical risk.

Two different syndromes exist: 1) ADE, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry. The mAbs in AZD7442 have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of ADE occurring via this mechanism should range from very low to none. 2) VAERD, which is a distinct clinical syndrome that occurred in young children in the 1960s when whole inactivated virus vaccines for measles and RSV were tested. Immunizing with limiting doses of RSV antigen, especially with conformationally incorrect antigens, can result in 2 major types of immunological phenomena: a) A relatively high ratio of antibody that binds, but does not neutralize, virus could potentially result in immunogenic cell death and complement activation (leading to inflammation and airway obstruction); b) immunization with whole inactivated virus vaccines can result in allergic inflammation characterized by, e.g., increased mucus production, airway hyperresponsiveness, and attenuated cytolytic T cell activity (T helper 2 cell immune response). This mechanism, induced by vaccines, should not be provoked by mAbs.

At present, there are no identified risks nor emerging safety profiles associated with AZD7442. The potential impact of the trial drug on other medicinal products including vaccines (including any SARS-CoV-2 vaccine) is not known. There is a possibility that receiving the trial drug prior to vaccination may result in the vaccine being less effective up to 9 months to 1 year or more or may cause a vaccine to have other currently unknown side effects.

No data are currently available to characterize the effects of giving AZD7442 to a person who has received a course of vaccination against SARS-CoV-2. Data from animal studies reported that prior AZD7442 administration did not alter either the cellular or the humoral immune responses elicited by subsequent SARS-CoV-2 vaccinations. Based on these results, AZD7442 is not anticipated to interfere with vaccine efficacy. More detailed information about the known and expected benefits and potential risks of AZD7442 can be found in the AZD7442 IB. There have been no events of anaphylaxis or other serious allergic reactions in the FTIH Phase I trial D8850C00001, D8850C00002 or D8850C00003 studies. There was one report of anaphylaxis: 1 (0.0%) participant in the AZD7442 group (classified as non-serious) in the PROVENT study.

6.1.3 Risk assessment of booster vaccines

Risk associated with the vaccine boosters also listed as IMPs within this trial are considered comparable to standard of care (Type A). It is not anticipated that the pre-dosing with AZD7442 would increase risks of the SARS-CoV-2 vaccines listed above.

6.1.4 Benefit Assessment

Recipients of AZD7442 do not have any guaranteed benefit. However, AZD7442 followed by SARS-CoV-2 vaccination may be efficacious and offer participants highly vulnerable to infection enhanced protection from SARS-CoV-2.

6.1.5 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this trial, the potential risks identified in association with AZD7442 and SARS-CoV-2 vaccination are justified by the anticipated benefits that may be afforded to participants at risk of SARS-CoV-2. This trial has been categorised as TYPE B, where the level of risk is somewhat higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 23).

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Patients will be identified and recruited at the participating hospital sites. Each participating site will:

1. Identified a suitably qualified PI
2. Be provided with protocol specific training before being activated for recruitment
3. Be provided with a local document package in line with HRA guidance (see HRA website: www.hra.nhs.uk). For sites in England this package will be provided simultaneously to both the trial delivery team and the research management team. For sites in Scotland and Wales the package will be provided as required by the devolved administrations.
4. Be provided with copies of the REC, HRA and competent authority (CA) approvals for the trial. The approval process includes granting favourable opinion of the host care organisation/PI.

Before any Site can begin recruitment, the following documents must be in place and copies sent to RAPID-PROTECTION@cardiff.ac.uk

1. Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
2. Favourable opinion of host care organisation/PI from Main Ethics committee
3. A signed Trial Agreement including MTA
4. Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
5. Completed Site Delegation Log and Roles and Responsibilities document
6. Full contact details for all host care organisation personnel involved, indicating preferred contact
7. A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s), and Withdrawal of Consent Form on host care organisation headed paper
8. A copy of the most recent approved GP letter and invitation letter on host care organisation headed paper
9. A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses
10. Returned Source Data Agreement signed by the PI.
11. Pharmacy confirmation that they have received the first shipment of IMP prior to opening the site.
12. Pharmacy confirmation that they have boosters available at site.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial drug supplies and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

All documentation must be stored in the Investigator Site File (ISF) at the site and in the Trial Site File (TSF) at the CTR. The CTR must be notified of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial files must contain this up-to-date information.

Site initiation will be by teleconference.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration.

Sites are encouraged to recruit a broad range of participant ethnic diversity and ages. PIs and sub-Is are encouraged to prioritise recruiting participants across a broad range of participant disease groups within each sub-cohort in order to obtain a reasonable breadth across each disease cohort. Recruitment into sub-groups will be regularly monitored by the trial team who may request that recruitment of particular disease sub-groups be paused. To support regular reporting of subgroup recruitment, we request that the baseline eCRFs and eligibility form is prioritised for data entry and that screening logs are updated regularly as per section 9.

8.1 Inclusion criteria

The participant must satisfy the following criteria to be eligible for the trial:

All participants

1. Provide written informed consent.
2. Previously completed SARS-CoV-2 vaccinations given as part of standard care at the time of enrolment.
3. Able and willing (in the Investigator's opinion) to comply with all trial requirements.
4. Willingness to practice continuous effective contraception during the first 3 months of the trial and, if appropriate, a negative pregnancy test on the day of screening.
5. Provide access to all medical records with respect to current and past medical treatments.
6. Have one or more of the following eligible conditions.

7. Adults ≥18 years

Eligible Conditions

Cohort 1: Haematological malignancies

Patients with a diagnosis of haematological malignancies and receiving one the following treatments:

- Cohort 1a - Patients receiving active therapy with immunosuppressive or immunomodulating agents including:
    - B-cell targeted therapies (rituximab or other anti-B-cell Ab therapy) used either as monotherapy or in combination with cytotoxic therapy in lymphoma / chronic lymphoproliferative disorders

    OR

    - JAK inhibitors (ruxolitinib or equivalent) in myeloproliferative neoplasms (MPNs)

    OR

    - ImiD drugs (thalidomide, lenalidomide, pomalidomide or equivalent) in myeloma and other plasma cell dyscrasias

    OR

    - BTK inhibitors (ibrutinib or equivalent) in chronic lymphocytic leukaemia / chronic lymphoproliferative disorders

    OR

    - Treatment within 24 months with lymphodepleting agents followed by chimaeric antigen receptor (CAR) T-cell therapy for any haematological malignancy

- Cohort 1b - Patients receiving aggressive therapy expected to cause temporary ablation of immune function including:
    - Acute leukaemia (AML or ALL) being treated with curative intent using intensive combination chemotherapy schedules (excluding acute promyelocytic leukaemia)

    OR

    - Patients within 24 months of receipt of allogeneic stem cell transplant or receiving systemic immunosuppression for graft versus host disease.

Cohort 2: Solid Tumours

- Early (Cohort 2a) or advanced cancer (Cohort 2b) (solid organ) undergoing systemic cancer treatment. Hormone treatments given alone such as tamoxifen or an aromatase inhibitor or LHRH agonist for early or advanced breast and prostate cancer are not considered to be a systemic treatment.

- Cancer patients are considered eligible for the trial if they have had a dose of systemic treatment within 42 days of trial entry.

Cohort 3: Renal/hepatic disorders

Cohort 3a - Renal Disorders:

Patients with kidney disease who fall into one of the following groups:

- Currently receiving immunosuppression
- Dialysis – including in-centre and home haemodialysis, peritoneal dialysis
- Transplant recipient receiving immunosuppression

Cohort 3b - Hepatic disorders:

- Patients with liver cirrhosis, autoimmune liver disease and liver transplant.

Cohort 4: Inflammatory disorders

- Patients receiving T-cell co-stimulation modulators, B-cell targeted therapies (including rituximab), tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors or JAK inhibitors
- Patients who had received any immunotherapies listed above in the previous 3 months for autoimmune diseases, except in the case of rituximab treatment within the previous 6-month period.
- Patients receiving or had received in the previous 6 months immunosuppressive chemotherapy
- Patients receiving systemic immunosuppression for a chronic inflammatory disorder.
- Cohort 4a will include participants receiving rituximab and cohort 4b will include participants receiving non-rituximab immunosuppressants

8.2 Exclusion criteria

The participant may not enter the trial if any of the following apply:

1. Significant infection or other acute illness, including fever > 100°F (> 37.8°C) on the day prior to or day of registration
2. Prognosis of less than 6 months.
3. ECOG Performance status of >2.
4. Planned receipt of any vaccine other than the trial intervention within 30 days before and after each trial intervention (day 0 and day 28) with the exception of the seasonal influenza

vaccination and non-COVID vaccinations in the case of patients receiving a haemopoietic stem cell transplant.

5. History of serious reactions likely to be exacerbated by any component of AZD7442 and SARS-CoV-2 vaccine.
6. Anaphylactic reaction following administration of a vaccine.
7. Known history of allergy or serious reaction to any component of the trial drugs formulation.
8. Patients who are pregnant or lactating at trial entry or planning to become pregnant within 3 months after AZD7442 administration.
9. Previous hypersensitivity, clinically significant infusion-related reaction, or severe adverse reaction following administration of a mAb.
10. Any prior receipt of other mAb indicated for the prevention or treatment of SARS-CoV-2 or COVID-19.
11. Clinically significant bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
12. Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the trial, affect the ability of the participant to participate in the trial, or impair interpretation of the trial data.
13. Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of trial follow-up, or concurrent participation in another interventional trial unless IMP is essential to clinical care*.
14. Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomization.
15. A history of hypersensitivity reactions including anaphylaxis and angioedema following administration of a SARS-CoV-2 vaccine.
16. A history of thrombocytopenia, including immune thrombocytopenia (ITP) following administration of a SARS-CoV-2 vaccine.
17. A history of Guillain-Barré Syndrome.
18. Patients with acute promyelocytic leukaemia.
19. Individuals with a known history of capillary leak syndrome (CLS).

*Please notify the trial team (RAPID-PROTECTION@cardiff.ac.uk) of any such instances

9 Recruitment, Screening and registration

9.1 Participant identification and screening

Highly immunocompromised patients may be identified by the recruiting sites through their clinical treatment team and multidisciplinary team. Additional patients can be identified by the research nurse from the patient notes. Participants may also be referred through their GPs and secondary care providers to participating sites. Similarly, patients involved in previous related studies may be approached by their treating team. Once patients have been identified as potentially suitable, patients

will be approached by a healthcare professional responsible for their clinical care for a referral to the site study team. The decision to accept this referral ultimately lies with each participating site.

The Eligibility Checklist should be completed prior to randomisation by the Investigator or clinical designee listed on the trial delegation log and recorded in the patient notes. This will include a pregnancy test for women who are of child-bearing potential.

Individuals being screened may or may not be eligible to receive a SARS-CoV2 vaccine booster as part of standard care at the time of being approached for the trial or during the trial. Scheduling of AZD7442 treatment may need to be considered should individuals being screened for the trial be due a SARS-CoV2 vaccine booster as part standard of care, to ensure they are given AZD7442 treatment at least 28 days after receiving the standard of care booster.

9.2 Screening logs

A screening log of all ineligible and eligible but not consented will be kept at each site so that any biases from differential recruitment will be detected. Separate screening logs will be used for each cohort at each site. When at site, logs may contain identifiable information, but this must be redacted prior to being sent to the CTR. The screening log should be sent to the RAPID-PROTECTION@cardiff.ac.uk every 2 weeks (see section 23 for further detail on data monitoring/quality assurance).

9.3 Recruitment rates

A total of 350 participants will be recruited across approximately 5 sites over a period of 3 to 6 months. Sites may be asked to pause randomisation across certain sub-cohorts to allow for a broad representation of disease types.

9.4 Informed consent

A full explanation should be given to the patients including the aims of the trial, what this will involve for the participant and possible adverse effects. This conversation should be structured around the Participant Information Sheet (PIS) and may be undertaken remotely. The patient information sheet may be sent to them in advance electronically or through the post prior to the meeting. The individual should be given adequate time (ideally 24 hours) to read the PIS, consider the trial and the opportunity to ask questions, before being asked to sign the Informed Consent Form (ICF). Consent may be taken by the local PI or a trained member of the trial team delegated to do so on the delegation log.

Informed consent will be obtained in writing by completing the consent form by both parties. One copy of the signed Consent Form to be given to the participant, and the original copy to be kept in the investigator site file and a further copy to be kept with the participant's hospital notes. Only when written informed consent has been obtained from the participant and they have been enrolled into

the trial can they be considered a trial participant. No trial procedures should be conducted prior to consent. Details of all patients approached about the trial should be recorded electronically on the Patient Screening/Enrolment Log (see section 9.2).

The right of the participant to refuse to participate in the trial without giving reasons must be respected. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

New safety information may necessitate changes to the PIS and ICF. In this event, it may be necessary to ask some, or all, participants to decide whether to re-consent or withdraw from the trial. Decisions on whether, and which, participants need to re-consent will be made by sponsor / TMG and the decision will be documented in the TMF. Timelines for the re-consent process to be completed will be set. The CTR will communicate local requirements to participating sites and initiate a process to track progress.

The participant's GP should be informed of their involvement in the trial. A template GP letter is provided electronically.

Trial and clinical data and samples will be shared with AstraZeneca and the wider trial team as part of the trial and may also be shared outside of the trial team for research purposes by national and international organisations. The data will be de-identified so that the participants cannot be identified outside of Cardiff University, AstraZeneca and the Sponsor through reasonable measures. Participants consenting to the trial will be consenting to future use of their de-identified data and samples in research outside of the trial under public interest. All research proposals will be reviewed by the CTR and Sponsor to ensure for scientific integrity and data and sample safeguarding.

Participants may also be asked to consent to NHS Information Centre Flagging (and Scottish and Northern Irish equivalents) so that the date and cause of death may be collected if not available. This will be optional and additional to the standard informed consent.

Participant consent is requested to collect NHS Numbers to utilise NHS data for future research, through Cancer Research UK and the National Cancer Intelligence Network (NCIN).

Participants will also be asked whether they are happy to be contacted about further information on the trial or other related studies. Information about the trial will be made available on the trial website.

9.5 Registration and randomisation

Once participants are identified, consented and deemed eligible, they will be assigned a unique trial ID and randomised by the treating team via the same portal. Participants will be randomised to receive one of two boosters in a 1:1 ratio:

Arm 1: Comirnaty bivalent (Original/Omicron BA.1)

Arm 2: Spikevax bivalent (Original/Omicron)

The trial will be unblinded and therefore both the participant and the site research team will know the treatment allocation. The trial pharmacist, research nurse and laboratory team will be notified of the randomisation allocation and trial ID number. A copy of the Randomisation Confirmation, signed Informed Consent Form, and Eligibility Checklist should be filed within the Investigator Site File.

Registration and Randomisation

Patient enrolment for this trial will be through the use of a web-based system:
https://trials.cardiff.ac.uk/portal

Details of how to access the system will be supplied to Investigators as part of the trial set-up.

If any problem with the web-based system or it is unavailable, please email the trial team:

RAPID-PROTECTION@cardiff.ac.uk

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial. In addition, a participant may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial medication
- Withdrawal of consent for treatment by the participant
- Any alteration in the participants condition which justifies the discontinuation of the treatment in the Investigator's opinion
- Non-compliance

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

- Withdrawal from AZD7442 or booster or both
- Withdrawal from further trial assessments

Data and samples collected from trial visits that have taken place up until the withdrawal date can still be sent but participant will not attend any further visits.

- Withdrawal from future research using excess participant samples
  Participants will have the option to destroy or keep samples collected prior to withdrawal date

- Withdrawal from future research using data
  Participants have the option to remove their consent to sharing of their de-identified data outside of the trial for future research.

- Withdrawal from any previous data to be used
  A participant can withdraw consent and request that their trial data is not used in the analysis of the trial. Since the legal basis for the processing of trial data is for scientific research purposes, which are in the public interest, and is subject to the necessary safeguards, any request for deletion of previous data collected will be reviewed by the trial TMG, who will consider whether the data should be processed or deleted. Previous reports and publications that use the participant's data will not be amended or deleted.

- Withdrawal from any previous sample to be used
  Participants may request that all previously collected samples are destroyed to prevent use in future research, though it may not be possible to retrieve samples already donated for future research e.g. If samples have been anonymised. Upon notification of a participant withdrawal via the relevant CRF form in the database, samples should be destroyed by the laboratory and noted on the destruction log.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly: If a participant wishes to stop taking part in the trial completely, they may need to be seen one last time for an assessment

If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for assessments and tests.

For participants who consent and subsequently withdraw their consent, the Withdrawal of Consent Form should be completed by the participant and signed by both the participant and the PI or a member of the trial team who has been delegated by the PI to undertake this activity. One copy of the Withdrawal of Consent Form will be given to the participant, the original copy will be kept in the ISF, and a further copy will be kept with the participant's hospital notes.

Completed participant withdrawal forms should not be sent to the CTR, since they will contain participant identifiable information. The participating site should advise the CTR of this withdrawal by completing the relevant Withdrawal form on the database.

Any queries relating to potential withdrawal of a participant should be forwarded to RAPID-PROTECTION@cardiff.ac.uk

10.2 Lost to follow up

Participants who withdraw from the trial or cease to attend trial visits prior to the end of the follow-up period will be classed as lost to follow up.

Every effort will be made to obtain follow-up information on these patients, unless they have completely withdrawn from the trial. Participants who are not present for a scheduled visit or follow up will be contacted by their local research team by telephone or letter. If they are contactable, the local research team will ask them to make an appointment to be seen at the next available clinic. If the participant declines or cannot be contacted, the local research team will inform their GP. If the participant is alive but not compliant with the approved visit schedule, the minimum information the local research team will aim to collect is the day 28 blood sample and visit assessment.

11 Trial Intervention

The following treatments are considered as IMPs within this trial:

- AZD7442 (Combination Monoclonal Antibody Product)
- Comirnaty bivalent (Original/Omicron BA.1) (Pfizer BioNTech)
- Spikevax bivalent (Original/Omicron) (Moderna)

Comirnaty bivalent Original/Omicron BA.1 and Spikevax bivalent (Original/Omicron)vaccines are approved for use under a conditional marketing authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012. Both vaccines will either be obtained through local supply or ordered from the UK Health Security Agency via the clinical trials unit. The initial supply of the vaccines will be triggered by the clinical trials unit upon receipt of all necessary approvals for the site. To order further vaccines, please contact RAPID-PROTECTION@cardiff.ac.uk.

There is no requirement for the vaccines to be labelled as IMP for this trial. Vaccine accountability will be in accordance with local Trust policy. Vaccine should be stored and prepared as specified in the Information for UK Healthcare Professionals. See the RAPID-PROTECTION Pharmacy Manual for additional information.

11.1 Dosing schedule

IMP	Dose	Route	Time point
AZD7442 (AZD8895 followed by AZD1061)	600 mg single dose of AZD7442 (300 mg of AZD8895 and 300 mg of AZD1061)	IM injection	Day 0
Comirnaty bivalent Original/Omicron BA.1: Arm 1	0.3ml containing 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles)	As per SPC	Day 28 (after day 28 bloods have been taken)
Spikevax bivalent (Original/Omicron): Arm 2	Spikevax: 0.5ml containing 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).	As per SPC	Day 28 (after day 28 bloods have been taken)

11.2 Treatment(s)

11.2.1 Comirnaty bivalent Original/Omicron BA.1

The SARS-CoV-2 vaccine BNT162b2, manufactured by Pfizer, is an mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. mRNA vaccines exploit the host's cells to make the target protein. In each dose, half of the vaccine encodes the original virus strain and the other half encodes Omicron.

One vial (2.25 mL) contains 6 doses of 0.3 mL. One dose (0.3 mL) contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran, a COVID-19 mRNA vaccine (embedded in lipid nanoparticles). The vaccine is a white to off-white frozen dispersion. Vaccine should be stored and prepared as specified in the SPC.

See the RAPID-PROTECTION Pharmacy Manual for additional information.

11.2.2 Spikevax bivalent vaccine (Original/Omicron)

The Spikevax bivalent (Original/Omicron) , manufactured by Moderna Biotech, is an mRNA (messenger ribonucleic acid (mRNA), vaccine which encodes for the SARS-CoV-2 spike protein. In each dose, half of the vaccine encodes the original virus strain from 2020 and the other half encodes the Omicron strain. The vaccine is supplied in multidose vials which contain 5 doses of 0.5ml each (100 doses per pack) and is a white to off white dispersion. Each dose is prepared by withdrawing 0.5ml from a vial in

a sterile 1ml or equivalent syringe as per government guidelines. Each 0.5ml dose contains 25 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles) and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).

Spikevax bivalent (Original/Omicron) vaccine has conditional marketing authorisation from the MHRA in Great Britain (consisting of England, Scotland and Wales).

See the RAPID-PROTECTION Pharmacy Manual for additional information.

11.2.3 AZD7442

AZD7442 is a combination of two Monoclonal Antibodies (mAbs) - Tixagevimab (AZD8895) and Cilgavimab (AZD1061) which were derived from B-cells donated by convalescent patients after SARS-CoV-2 virus infection. The human monoclonal antibodies bind to distinct sites on the SARS-CoV-2 spike protein (Dong et al, 2021). The SARS-CoV-2 spike protein contains the receptor-binding domain (RBD), which enables the SARS-CoV-2 virus to bind to receptors on human cells. By targeting the RBD region of the virus's spike protein, AZD7442 block the virus's attachment to human cells to prevent infection.

11.2.4 AZD7442 Dosage, scheduling and packaging

A single 600 mg dose of AZD7442 consists of injections (divided into sequential injections for each mAb component). If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the next IM injection, the next IM injection should not be given. For details on the treatment of anaphylactic reactions after IMP IM injections see Section 11.3.

Table 2 Investigational Products

Intervention name	AZD7442 (Tixagevimab AZD8895 + Cilgavimab AZD1061)
Dose formulation	Liquid Product AZD7442 will be supplied as separate vials of AZD8895 and AZD1061 as 150 mg colourless to slightly yellow, clear to opalescent solutions for injection. The solutions contain 100 mg/mL of active ingredient (AZD8895 or AZD1061) in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. The label-claim volume is 1.5 mL
Unit dose strength(s)	600 mg AZD7442 consisting of 300 mg AZD8895 and AZD1061 at 100 mg/mL
Dosage level(s)	600 mg single dose of AZD7442 (300 mg of AZD8895 and 300 mg of AZD1061)

Route of administration	AZD7442 IMP is comprised of 2 separate drug products, AZD8895 and AZD1061, to be administered as IM injections sequentially as per Pharmacy Manual.
Use	Experimental
Sourcing	AZD7442 (AZD8895 + AZD1061): Provided by AstraZeneca
Packaging and labelling	IMP will be provided in a glass vial. Each glass vial will be labelled as required per MHRA requirements.

See the RAPID-PROTECTION Pharmacy Manual for additional information.

Preparation/Handling/Storage/Accountability

- Each vial selected for dose preparation should be inspected. If there are any defects noted with the IMP, the investigator and trials unit should be notified immediately.
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received, and any discrepancies are reported and resolved before use of the IMP.
- Only participants enrolled in the trial may receive IMP and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused IMPs are provided in the Pharmacy Manual or specified handling instructions.

AZD7442 Dose Preparation and Administration Instructions

Dose Preparation Steps

The 2 drug products AZD8895 and AZD1061 (comprising AZD7442), must both be administered separately to the participant in sequential order, with no participant receiving doses of AZD8895 without also receiving the matching dose of AZD1061. The dose of AZD8895 must be administered first. The dose of AZD8895 and AZD1061 for administration must be prepared by the IMP Manager or other qualified professional using aseptic technique, and who should only remove the required DP vials for participant dosing from storage. AZD8895 and AZD1061 should be administered according to standard practice procedures for IM injections. Please refer to the Pharmacy Manual for further details.

Post dose administration

An inspection of the injection site should be performed on the day of treatment as per table 3 below;

Table 3: Injection Site Inspection on Day 1

Procedure/Time after both injections have been administered	Immediately after IMP administration	15 minutes
Visual inspection of site	x	x
Palpation of site	x	x
Participant will be asked "Are you experiencing any discomfort?"	x	x
If yes, has the feeling of discomfort changed since you received the injection?		x

Any AEs should be reported as per section 14

11.2.5 Dose modification for toxicity

The IMP will be administered as described in Section 11 and the Pharmacy Manual. Dose modification is not permitted.

11.3 Management of toxicity and hypersensitivity reactions

Table 4: An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions

Severity of symptoms	**Treatment**	**Investigational product**
Mild local reactions (During and post injection and hypersensitivity) Mild injection	Evaluate participant, including close monitoring of vital signs. At the discretion of the	Pause or hold additional IMP injection immediately. At the discretion of the Investigator,

site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localised at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mmHg change in systolic BP from pre-administration measurement.	Investigator, treat participant, for example, with: Localized cold pack or heat to the injection site. If more generalized reaction: • Diphenhydramine 50 mg PO or equivalent and/or • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or • Topical antihistamines and/or low-potency topical corticosteroid preparations and/or • Anti-nausea medication, as needed.	resume current IMP administration under observation.
Moderate reactions (during or immediately post injection) Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below).	Evaluate participant, including close monitoring of vital signs. Treat participant, for example, with: • Normal saline (~500 to 1000 mL/hour IV) • and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or • Anti-nausea and/or antiemetic intramuscular, as needed.	Stop or hold additional IMP administration immediately. At the discretion of the Investigator, resume current IMP administration under observation.
Severe Above plus fever with rigors, hypo- or hypertension with ≥40 mmHg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope, incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor OR Life-threatening (Defined as a reaction that is life-threatening	Evaluate participant, including close monitoring of vital signs. Maintain airway, oxygen if available. Treat participant immediately, for example with: • Normal saline (~500 to 1000 mL/hour IV) Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0	Stop IMP administration immediately. Do not resume current dosing. Permanently discontinue IMP administration. Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days.

and requires pressor and/or ventilator support or shock associated with academia and impairing vital organ function due to tissue hypoperfusion)	mL administered SC for mild cases and intramuscular for more severe cases IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine Grade 4 event at the discretion of the investigator	

11.4 Overdose

For this trial, any dose of AZD7442 > 300 mg of either individual mAb will be considered an overdose. There is no recommend specific treatment for an overdose. Symptoms of overdose should be treated as per clinical judgement.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module. If an overdose of AZD7442 occurs in the course of the trial, then the PI or other site personnel inform appropriate trial representative immediately, but no later than 24 hours of when he or she becomes aware of it.

The designated trial representative works with the PI to ensure that all relevant information is provided to the data entry site within 1 or 5 days for SAEs, and within 30 days for other overdoses.

Any overdose of Pfizer BioNTech (BNT162b2) and the Moderna (mRNA-1273) vaccines should be managed according to the SPC and local clinical practice protocols.

11.5 Pre-medication

No pre-medications are required before treatment with AZD7442, Spikevax bivalent (Original/Omicron) and Comirnaty bivalent (Original/Omicron BA.1).

11.6 Permitted, Restricted, and Prohibited Medications

Permitted, restricted, and prohibited medications are summarized in Table 5. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the trial must be recorded, along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Trial Physician should be contacted if there are any questions regarding concomitant or prior therapy

Table 5: Permitted, restricted and prohibited medications

Use Category	Type of medication/treatment	Timeline/instructions
Permitted	Routine Vaccines	Licensed influenza vaccines are permitted at any time. All other routine non-COVID vaccines are permitted beginning > 30 days after IMP dose with the exception of patients receiving a haemopoietic stem cell transplant who may receive non-COVID vaccines at any time.
	Allergen immunotherapy	Allowed if participant has been receiving stable therapy for at least 30 days prior to Visit 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as IMP

	Commercial biologics, prednisone, immunosuppressive medications (e.g., azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy, immunotherapy or targeted treatment for cancer)	Allowed, provided the participant is stable on maintenance dose (at steady state) prior to Visit 1, and must not be administered on the same day as IMP
	Participants may take concomitant medications prescribed by their primary care provider or hospital team for management of chronic medical conditions and/or for health maintenance. Primary care providers or hospital providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the trial. Participants who develop COVID-19 after receiving IMP should be treated according to local standard of care, including investigational agents within a clinical trial setting.	
Prohibited	Not applicable	Not applicable
Restricted	Contraceptive methods	**See section 14.8**
	Blood/plasma donation	Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after dose of study drug, i.e. one year.
	Standard of care COVID-19 vaccines	Participants must not obtain standard of care approved COVID-19 boosters until at least 3 months after receiving their vaccine booster on this study unless the study team specifically advise otherwise.

11.6.1 Trial restrictions- contraception

Participants must follow the contraception requirements outlined in section 14.8.

11.7 Accountability procedures

Local pharmacy personnel will be responsible for ensuring that the IMP is managed and dispensed to participants in accordance with the duly approved current protocol.

Accountability logs for AZD8895 and AZD1061 are included in the Pharmacy Pack provided by CTR upon site activation.

Trial specific accountability is not required for vaccines.

The investigator is responsible for keeping accurate records of the clinical supplies received from AstraZeneca or designee, of the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the trial, all unused and/or partially used investigational product will be destroyed at the site per institutional policy after authorisation from CTR. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

12 Sample Management

Sites will be provided with a translational sample collection kit. Up to 50ml of blood will be collected from participants at the following timepoints:

- Baseline (Predose)
- 28, 56, 112 and 180 days post AZD7442

Samples will be processed and frozen onsite. The CTR will arrange regular batch collections of samples on dry ice to the relevant Laboratory. Samples may be stored by laboratories approved by the Sponsor.

A subset of sites will be asked to provide fresh samples for additional analysis. Full details on sample collection and management can be found in the Laboratory Manual.

Lateral flow tests for SARS-CoV-2 infection will be performed for a subset of participants routinely on day 0, 28, 56, 112 and 180. If the lateral flow test is positive for SARS-CoV-2 infection, a nasal PCR swab will be taken to be sent for testing.

All participants testing positive to SARS-CoV-2 throughout the trial will also be asked to send a nasal PCR swab for testing.

12.1 Analysis

Immunogenicity will be assessed by a variety of immunological assays at University of Oxford research laboratories or at designated specialist laboratories. This will include:

- Quantify antibody responses to SARS-CoV-2 Spike and non-Spike antigens
- Assessment of T-cell responses using ex vivo ELISpot assays for interferon gamma and flow cytometry assays or other relevant assays of cellular function and phenotype.
- Assessment of neutralising antibody against live and/or pseudotype SARS-CoV-2 virus variants
- B cell analyses, and Peripheral blood mononuclear cell (PBMC) analysis.

Serology and PK analysis will be conducted at research laboratories as specified in the Laboratory Manual according to laboratories SOPs.

A subset of participants will be regularly tested for SARS-CoV-2 infection. All samples positive for SARS-CoV2 infection will be sequenced to identify escape variants.

DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity and/or SARS-CoV-2 pathogenesis or SARS-CoV-2 therapeutics and gene expression studies amongst others may be performed at the discretion of the Investigators.

This is not an all-inclusive list: additional assays will be performed as more information becomes available about the immune response elicited during the trial.

Should a participant have a SARS-CoV-2 infection, severity should be assessed using the WHO Clinical Progression Scale (see Appendix 2).

12.1.1 Biobanking

Participants will be informed that there may be leftover samples of their blood (after all testing for this trial is completed), and that such samples may be stored indefinitely for possible future research (exploratory immunology) will be able to decide if they will permit such future use of any leftover samples. With the volunteers' informed consent, any leftover cells and serum/plasma will be frozen indefinitely for future analysis of SARS-CoV-2 and other coronaviruses related diseases or vaccine-related responses. If a subject elects not to permit this, all of that subject's leftover samples will be discarded after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements. Samples that are to be stored for future research will be transferred to the Oxford Vaccine Centre (OVC) Biobank (REC 16/SC/0141) or equivalent Human Tissue Authority (HTA) licenced biobank.

13 Trial procedures

Appointments that do not require clinical intervention can be taken by phone where possible to limit participant's exposure. This may include questionnaires that can be emailed or posted where this remains in the best interest of the participant. The participant should be approached by the treating team to ensure that they are happy to be contacted in this way.

Table 6 summarizes the trial procedures to be performed at each visit by the PI or qualified designee. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points, if deemed clinically necessary by the investigator.

Where possible, participants' visits should be aligned with their routine visits.

13.1 Assessments

Baseline Assessments

All baseline assessments should be performed after consent has been obtained and within 28 days of treatment. Participants will be required to attend clinic for blood sample collection and treatment. The following assessments will need to be done:

- Completion of eligibility checklist form
- Participant informed consent
- Full Medical History
- Randomisation as per Section 9.5 of the protocol
- Participants should be asked about their previous SARS-CoV-2 vaccination history. The information should be collected on the SARS-CoV-2 vaccine form.
- Prior and Concomitant Medications Review of any medications received within 28 days before the first dose of trial treatment
- Participant behavioural questionnaires (risk behaviour changes, PROMIS 10, EQ-5D-5L)

AZD7442 treatment (this can be done on the same day as baseline assessments)

Day 0

- A negative urine dipstick pregnancy test should be performed to confirm eligibility for women of child-bearing potential.
- Toxicity assessment (CTCAE 5.0)
- Blood sample collection and completion of the sample eCRF
- Safety bloods (full blood count (FBC), Urea and electrolytes (U&E), Liver function test (LFT) and bone profile)
- Full Physical Examination including vital signs, weight and height
- Blood sample collection prior to AZD7442 dosing and completion of the sample eCRF
- Routine (asymptomatic) lateral flow testing for SARS-CoV-2 infection (only subset of participants). If the lateral flow test is positive for SARS-CoV-2 infection, a nasal PCR swab should be taken to be sent for testing.

NB: The assessments above should be performed ***before*** the administration of AZD7442.

- Dosing with AZD7442

On Day 14 post AZD7442 (+/- 3 days):

- Toxicity assessment via telephone consultation with patient to check on symptoms.

On Day 28 post AZD7442 (+/- 3 days):

- Clinical review
- Vital signs
- Blood sample collection and completion of the sample eCRF
- Safety blood samples (FBC, U&E, LFT and bone profile)
- Concomitant Medications Review
- Toxicity assessment (CTCAE 5.0)
- Routine (asymptomatic) lateral flow testing for SARS-CoV-2 infection (only subset of participants). If the lateral flow test is positive for SARS-CoV-2 infection, a nasal PCR swab should be taken to be sent for testing.

NB: The assessments above should be performed ***before*** the administration of SARS-CoV-2 vaccine booster.

- SARS-CoV2 vaccine booster administration as per randomisation allocation. This should be given 28 days (+/- 3 days) post AZD7442.

Follow-up Assessments (+/- 3 days for day 56 assessment and +/- 7 days for day 112 and 180, assessments):

The follow up assessments at Day 56, 112 and 180 (post AZD7442) include:

- Clinical review (Day 56,)
- Vital signs (Day 56)
- Concomitant Medications Review (Day 56, 112 and 180)
- Toxicity assessment (Day 56)
- Blood samples collection (Day 56, 112 and 180)
- Safety blood samples (FBC, U&E, LFT and bone profile) (day 56 and 180)
- Routine (asymptomatic) lateral flow testing for SARS-CoV-2 infection (day 56, 112 and 180) (only subset of participants). If the lateral flow test is positive for SARS-CoV-2 infection, a nasal PCR swab should be taken to be sent for testing.
- Participant behavioural questionnaires (risk behaviour changes, PROMIS 10, EQ-5D-5L) (day 112 and 180)

13.1.1 Reduction of follow up period

The Food and Drug Administration (FDA) released an announcement at the end of January 2023 advising that the use of Evusheld should be limited to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90 %. The non-susceptible SARS-CoV-2 variants included the XBB, CH.1.1 and BQ.1 sub-lineages of the Omicron variant. At this time in the U.S., fewer than 10 % of circulating variants were susceptible to Evusheld, so the FDA removed the use of Evusheld until further notice in the U.S. The link below provides further information regarding this announcement: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us

At this time the UK had not yet reached a threshold where ≥ 90 % of the circulating variants were Evusheld-resistant SARS-CoV-2 variants so the decision was made to continue the trial as planned but closely monitor the data published weekly by the Office for National Statistics (ONS).

After monitoring the data on the UK SARS-CoV-2 infection survey that was published by the ONS over the following months, the decision was made to pause recruitment within the RAPID-PROTECTION study at the beginning of April 2023, since the percentage of circulating Evusheld resistant SARS-CoV-2 variants had exceeded the 90 % threshold. The decision was also made to reduce the follow-up period from 12 months to 6 months for all patients.

A Changes to Follow up Notification form has been created to notify existing participants of these changes and this should be provided to all participants as soon as possible.

13.2 Not permitted during the study

Additional vaccines may affect the results of the study and not give an accurate picture of the protection provided by Evusheld. Unless the study team specifically advise otherwise, participants are not permitted to receive any of the approved NHS SARS-CoV-2 vaccinations for 3 months after their SARS-CoV-2 vaccination within the study.

13.3 Ad hoc assessments

Cases of confirmed SARS-CoV-2 should be documented within the CRF. Should a participant have a COVID-19 infection, COVID-19 severity should be assessed using the WHO Clinical Progression Scale (see Appendix 2). Participants testing positive should be reminded to take and send a nasal PCR swab sample for sequencing analysis to monitor for escape variants.

Table 6. Schedule of enrolment, interventions and assessments

Procedures	**Visits**						
	Baseline†	**Treatment Phase**			**Follow Up**		
		Day 0	Day 14	Day 28	Day 56	Day 112	Day 180
Informed consent	x						
Medical history	x						
Clinical review				x	x		
Inclusion/Exclusion criteria	x						
Physical examination		x					
Vital signs (including height and weight)		x		x	x		
Concomitant Medications Review	x			x	x	x	x
Toxicity assessment		x	x***	x	x		
Urine pregnancy test	x						
Blood sample collection		x*		x	x	x	x
Safety blood sample (FBC, LFT, bone profile and U&E)		x*		x	x		x
AZD7442 administration		x					

SARS-CoV-2 vaccine administration				x			
Routine (asymptomatic) lateral flow testing for SARS-CoV-2 infection**		x		x	x	x	x
COVID-19 infection severity (where applicable)			x	x	x	x	x
Participant questionnaires (risk behaviour changes, PROMIS 10, EQ-5D-5L)	x					x	x

† Within 28 days prior to AZD7442 administration

* Sample collected prior to AZD7442

** Lateral flow testing for SARS-CoV-2 infection to be performed for a sub-set of participants. If the lateral flow test is positive for SARS-CoV-2 infection, a nasal PCR swab will be taken to be sent for testing.

*** Toxicity assessment can be done via telephone call with the participant

14 Pharmacovigilance

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 14.2). This includes SAEs related to IMPs.

14.1 Definitions

Table 7: definitions of pharmacovigilance terms

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that – 1. Results in death 2. Is life-threatening* 3. Required hospitalisation or prolongation of existing hospitalisation** 4. Results in persistent or significant disability or incapacity 5. Consists of a congenital anomaly or birth defect 6. Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that use or continued use of the product would result in the participants death; it does not refer to an event which hypothetically might have caused death if it were more severe.

** **Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements defined in Table 7, for the purposes of this trial the following events will also be considered adverse events of special interests (AESI) and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Anaphylaxis and other serious hypersensitivity reactions including immune complex disease (defined by regulatory criteria of seriousness and MedDRA SMQ Hypersensitivity (Narrow)) – Grade 3 and above
- Cardiac events (i.e. cardiac ischemia, cardiac failure and thrombotic events)
- Injection site reactions (defined by MedDRA HLT Injection site reactions) – grade 3 and above
- SARS-CoV-2 infections requiring hospitalisation, life threatening or death within start of treatment and 28 days following vaccine booster. Following the 28 days, reporting of these events are to be captured on the relevant eCRF.

For the purposes of this trial the following events will not require reporting as SAEs:

Hospitalisations for:

- Disease treatment
- Receipt of supportive care for disease treatment related toxicities (e.g. neutropenic sepsis, vomiting for cancer participants) (unless there is concern this has been exacerbated by vaccination)
- Disease progression (unless there is concern this has been exacerbated by vaccination)
- Pre-planned elective procedures (unless the condition worsens)
- Injection site reactions (defined by MedDRA HLT Injection site reactions) – grade 2 and below
- Anaphylaxis and other serious hypersensitivity reactions including immune complex disease (defined by regulatory criteria of seriousness and MedDRA SMQ Hypersensitivity (Narrow)) – Grade 2 and below

Pre-existing conditions should only be reported if they meet the definitions for an SAE and if the condition worsens by at least one CTCAE grade.

Pre-existing conditions should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.

14.3 Causality

Causal relationship will be assessed for IMPs, other trial treatments (nIMPs) and procedures:

Table 8: IMPs

AZD7442 (Combination Monoclonal Antibody Product)
Comirnaty bivalent (Original/Omicron BA.1) vaccine (Pfizer BioNTech)
Spikevax bivalent (Original/Omicron) vaccine (Moderna)

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 9: Causality assessment

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the IMP?**
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the	Yes

	participant's clinical condition, other concomitant treatments).	
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

14.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the NCA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Table 10: list of sources of RSI for each IMP.

IMP	**RSI to be used for expectedness assessment**	**Relevant section to be used for expectedness assessment**
AZD7442 (Evusheld)	IB, AstraZeneca	Section 5.6
Comirnaty bivalent (Original/Omicron BA.1)	Pfizer SPC/BioNTech – bivalent vaccine Comirnaty Original/Omicron BA.1	Section 4.8
Spikevax bivalent Original/Omicron	Spikevax bivalent SPC	Section 4.8

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

14.5 Reporting procedures

14.5.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number and year of birth. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number:

0203 0432 376

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 28 days after the participant receives their last dose of the IMP. Serious adverse reactions (such as long term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol.

Serious Adverse events (SAE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An Adverse Event / Adverse Reaction

- IMP or trial intervention
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

14.5.2 CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 28 days after the participant receives their last dose of the investigational medicinal product. Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA, Main Ethics Committee and AstraZeneca.

14.6 SUSAR reporting

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs and relevant ethics committees) and to AstraZeneca as follows:

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.

If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening and non-life-threatening SUSARs.

Any additional, relevant information must be reported within a further 15 days.

14.7 Safety Reports

A list of all SAEs and SARs (expected and unexpected) will be reported annually to the MHRA, REC, trial sponsor and AstraZeneca in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA Clinical Trial Authorisation (CTA) approval date.

The CTR will report a list of all SAEs and SARs (expected and unexpected) and any other safety recommendations to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

14.8 Contraception and pregnancy

14.8.1 Definitions

Women of Non-Childbearing Potential

Women of non-childbearing potential are defined as female participants who are permanently surgically sterilized or postmenopausal. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy at least 6 weeks before screening. Bilateral oophorectomy alone is acceptable only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

For women aged < 50 years, postmenopausal is defined as having both a history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment, and an FSH level in the postmenopausal range. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential.

For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Women of Childbearing Potential (WOCBP)

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile.

Pregnancy Testing Women of childbearing potential can be included only after a negative urine pregnancy test. Urine pregnancy testing will be done as per the SoA (see Section 13). If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.

14.8.2 Contraception

Women of Childbearing potential

AZD7442 in this trial has a demonstrated or suspected human teratogenicity/fetotoxicity. Women of childbearing potential who are sexually active must agree to use, with their non-sterilized male partner, an approved method of highly effective contraception from the time of AZD7442 administration until 3 months after. In instances where a WOCBP has a sterilized male partner, the vasectomized partner must have received a medical assessment of surgical success. Women should be stable on their chosen method of birth control for at least one month before dosing. Highly effective contraception is summarized in Table 11.

Table 11: Highly effective methods of contraception

Barrier method	Hormonal method

• Intrauterine device
• Intrauterine hormone-releasing system (IUS)[a]
• Bilateral tubal occlusion
• Vasectomized partner [b]
• Sexual abstinence [c]
	• Combined (oestrogen- and progestogen-containing hormonal contraception) associated with inhibition of ovulation
	  ○ Oral (combined pill)
	  ○ Intravaginal
	  ○ Injectable
	  ○ Transdermal (patch)
	• Progestogen-only hormonal contraception associated with inhibition of ovulation
	  ○ Oral
	  ○ Injectable
	  ○ Implantable

a This is also considered a hormonal method. b Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success. c Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period from the time of AZD7442 administration until 3 months after and if it is the preferred and usual lifestyle of the participant.	

Male Participants

To avoid transfer of fluids to a sexual partner, all male participants must use a condom starting from the time of AZD7442 administration until 3 months after. Contraception for female partners of childbearing potential may be considered, but is not required for this protocol.

Participants will be instructed that if their partner becomes pregnant in the three months following AZD7442 administration, this should be reported to the PI. The PI should also be notified of pregnancy occurring within 3 months of AZD7442 administration but confirmed after completion of the trial. In the event that a participant's partner is subsequently found to be pregnant within 3 months of the participant receiving AZD7442, then consent will be sought from the partner and, if granted, any pregnancy will be followed, and the status of mother and/or child will be reported to the Sponsor after delivery. A pregnancy notification form and follow-up will be completed.

14.8.3 Donation

Ova Donation

Female participants should not donate ova for at least 3 months after the AZD7442 dose.

Sperm Donation

Male participants should not donate sperm for at least 3 months after the dose of AZD7442.

14.8.4 Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Pregnancy occurring within 3 months of AZD7442 administration and reported during the trial will be followed up for safety from the post-dose administration to end of the trial, or until term, to identify pregnancy outcome, whichever is later.

Female participants who become pregnant after dosing will continue to have all PK samples collected. These do not represent a safety risk. Any complications during the planned follow-up of any pregnant

participant (if any) will be discussed between the PI and AstraZeneca, and a decision to halt or continue any further sampling will be made on a case-by-case basis.

15 Statistical considerations

15.1 Randomisation

Participants will initially be enrolled and registered for the trial and all will receive the trial treatment AZD7442. At 28 days of follow up participants will subsequently be randomised in a 1:1 ratio to one of the two booster vaccines (Spikevax bivalent (Original/Omicron) and Comirnaty bivalent (Original/Omicron BA.1)). A computer-based randomisation allocation process will use random permuted blocks of varying sizes. The trial statistician will produce the randomisation schedule prior to enrolling participants.

15.2 Blinding

This is an open label trial.

15.3 Sample size

We aim to recruit a total of 350 patients with immunosuppressive conditions. Sample sizes required for analysis of the various groups and outcomes have been based on SARS-COVID-2 IgG responses taken from the analysis of the PROVENT trial and other similar trials.

To compare Groups 1 + 2 + 3 + 4 with healthy volunteers from the PROVENT trial to show a reduction in IgG levels at 90% power with a 5% significance of 0.5 (log domain) and SD of 1 we need 70 patients. We expect this consideration to show that the variance in IgG levels is larger than healthy volunteers and have therefore powered to allow for the same comparison in each of the four sub-groups (1, 2, 3, 4) – 70 per group to give a total of 280 required. Allowing for loss to follow-up of 20% we will aim to recruit 350 patients stratified across the selected groups. To maximise heterogeneity at the group level and improve branching decisions, we will target even recruitment numbers in the subgroups of each group (level 3 in figure 2).

Analysis of the identified groups 1 + 2 + 3 + 4 will be undertaken once 280 completed datasets at 28 days have been achieved. If the variance in IgG levels is shown to be significantly different to healthy controls or more variable, then the analysis will progress to groups 1, 2, 3, and 4 individually and recruitment targets re-estimated.

15.4 Missing, unused & spurious data

Detail will be provided in the Statistical Analysis Plan (SAP).

15.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.6 Termination of the trial

There are no formal statistical stopping rules for termination of the trial. The IDMC will assess safety and efficacy data on an ongoing basis and will report to the TSC any concerns that would merit investigating the potential termination of the trial.

15.7 Inclusion in analysis

All enrolled participants will be included in analyses.

16 Analysis

A detailed Statistical Analysis Plan will be produced prior to the database lock. In general, a treatment policy approach to estimands will be used to deal with intercurrent events.

16.1 Main analysis

16.1.1 Immunogenicity at 28 days following administration of AZD7442

The function and magnitude of SARS-CoV-2 specific antibody and T cell responses will be measured at baseline and at additional multiple timepoints after the administration of AZD7442. The immunological effect of the study interventions will be determined by comparison of the results of immunological assessments at baseline and subsequent time points.

Assays will quantify the amount of serum antibodies to 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. Ab function, including viral neutralisation will be assessed.

The magnitude and function of SARS-CoV-2 specific T cell responses following the booster vaccination will use assays that give insight into T cell function. Laboratories will measure neutralizing antibodies to SARS-CoV-2 using validated wild-type neutralization assay or pseudo-neutralization assays.

Comparisons of immunogenicity outcomes will be made with age and gender matched healthy controls from the PROVENT III trial. Group data will be requested from the PROVENT trial. Values will be log-transformed and mean and standard deviation calculated for the same groups at each timepoint. The PROVENT data will be used to calculate the overall standard deviation of a population with the same age / sex distribution as each of our cohorts at each timepoint. The mean and standard

deviation and its 95% confidence interval will be calculated for each cohort for comparison with the PROVENT data at each timepoint.

The ratio of the variances in the log transformed domain will be tested to assess if it is significantly different from 1. All tests will be one sided and focussed on if the trial patients perform less well than the healthy volunteers in terms of response to vaccine. Results will be reported as the ratio of variances, 95% confidence intervals and p values.

16.1.2 Immunogenicity at 28 days following administration of AZD7442 followed by a SARS-CoV-2 vaccine 28 days later (outcome measured at day 56)

To assess if treatment with AZD7442 followed by a SARS-CoV-2 vaccine 28 days later will increase levels of anti-SARS-COVID-2-anti S-RBD neutralising antibodies in patients. This will be assessed in a hierarchical way firstly comparing age-matched healthy controls from the PROVENT III trial of the AZD7442 and AZD1222 all patients (groups 1, 2, 3 and 4) on both point estimator and variance and if the variance is greater than subdividing into the individual groups by patient group.

Comparisons will be made between each of the vaccines using an ANCOVA model with baseline value as a covariate. An exploratory analysis will be conducted to examine differences between the vaccine types and patient cohorts (see section 16.3 below).

16.1.3 Analysis of SARS-CoV-2 infection

Incidence of SARS-CoV-2 infection will be a descriptive analysis and summarised by incidence rates and 95% confidence intervals. Comparison of incidence rates between groups will be performed using Poisson regression and summarised as Incidence rate ratios, risk differences, 95% confidence intervals and p values.

16.1.4 Analysis of Patient Questionnaires

Patient questionnaires will be summarised using frequencies and proportions. For continuous measures, e.g., EQD visual analogue scale (VAS) responses will be summarised using means, standard deviations, medians and interquartile ranges. Differences in responses for questions between groups will be assessed using the Wilcoxon-Mann-Whitney test. Changes in responses over time will be examined using multilevel models accounting for the longitudinal nature of the data. Full details will be provided in the SAP.

16.1.5 Analysis of PK data

PK data will be processed by the laboratory and summarised graphically with concentrations and standard deviations reported at each time point. Full details of the statistical analysis methods will be provided in the SAP.

16.1.6 Safety Analysis

Incidence of adverse events will be calculated as incidence rates with 95% confidence intervals. Confidence intervals will be calculated using exact Poisson methods as it is anticipated they will be relatively rare. Incidence rates will be calculated for each category of MedDRA coded preferred term (PT) and then aggregated to system organ class (SOC). In addition, serious adverse events will be categorised by PT and SOC and be presented as a detailed listing.

16.2 Sub-group & interim analysis

There are no planned sub-group analyses other than those described in the main analysis for the trial adaption process. Interim analyses are planned every 120 days and will consist of safety data reporting as described in the main analysis section.

16.3 Exploratory analyses

Exploratory analyses will be performed by examining the immunogenicity response and stratifying by the following variables:

- Covid-19 vaccine type used as a booster at 28 days post treatment with AZD7442. This will be assessed at day 56, that is 28 days after the booster vaccine is administered. Where sufficient participant numbers are available further stratification by participant cohort, that is the interaction of vaccine type and participant cohort, will also be conducted. This analysis will use the same regression model as the main analysis but include an interaction term in the model to describe the vaccine type and patient cohort combinations.

Where sufficient data is available, regression models will be constructed to examine factors associated with immunogenicity response. In addition, should infections undergo an increase during the study then this may allow an analysis of any link between immunogenicity response and infection; as well as an analysis of the SARS-CoV-2 severity using the WHO Clinical Progression Scale comparing differences in the study cohorts.

17 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

Source documents include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. Sites will retain all original source data from these investigations for future reference. On all trial-

specific documents, other than the signed consent form, the participant will be referred to by the trial participant ID, not by name.

17.1 Completion of CRFs

CRFs

It is intended to develop data recording for this trial as a web-based system. This is a secure encrypted system accessed by an institutional password and complies with the General Data Protection Regulation standards.

Details of how to access the system will be supplied to investigators as part of site set up. A user password will be supplied to investigators upon completion of all processes required prior to opening.

Participating sites will be provided with training and instructions on how to complete and return the CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

Data linkage

The participant's NHS number will be collected to allow linkage with national data registries such as NHS Digital, Public Health England, HCRW and the Information Services Division (part of NHS Scotland), or the electronic Data Research and Innovation Service (eDRIS). Data linkage will allow for long-term follow-up data to be collected and it will provide a more complete profile of the participants' health and disease without increased data collection burden to the NHS.

18 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

19 End of Trial definition

The treatment phase will be followed by a follow-up period which will continue for 6 months after the last participant completes protocol treatment.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the act of entering the final data onto the trial database.

Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

20 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 25 years or longer, if deemed necessary for participants' safety and/or new regulatory requirements. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 CTA

The trial is being performed under a CTA from the MHRA. The CTA, the approval of the MHRA, has been obtained before the start of the trial in accordance with Part 3, Regulation 12 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031).

21.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol has been submitted through Health Care Research Wales which assesses governance and legal compliance for the NHS in Wales. Additional governance review and approval has been obtained through HRA as this is required to open sites in England. The HRA approval process replaces the need for local checks of legal compliance and related matters by participating sites in England—this means sites do not give site specific governance approval.

In Wales, approval has been obtained from the host care organisation who consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

Participating sites are required to confirm their capacity and capability to deliver the trial.

Substantial amendments to this Protocol must be approved by the MREC responsible for the trial and MHRA (where applicable), before the implementation of the amendments. Minor amendments will not require prior approval by the REC and MHRA.

If the trial is temporarily halted, it will not be recommenced without reference to the REC responsible for the trial and the MHRA.

The REC and MHRA will be notified within 90 days of trial completion. If the trial is terminated early, the REC and MHRA will be notified of this within 15 days.

A summary of the clinical trial report will be submitted to the MREC responsible for the trial and MHRA within one year of the end of trial.

21.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian and the translational sample custodian for this trial is the Sponsor and CI respectively.

This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with the HSCIC.

Representatives of the Sponsor, AstraZeneca or regulatory authorities will be given access to trial data and trial documents (at sites or the CTR) for monitoring or inspection purposes. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

21.4 Indemnity

1. Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

2. Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

21.5 Trial sponsorship

Cardiff University will act as Sponsor for the trial. Delegated responsibilities will be assigned to the sites taking part in this trial.

The trial is being sponsored by Cardiff University with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research
- The General Data Protection Regulation 2016
- The Human Tissue Act 2004
- Other regulatory requirements as appropriate

The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

21.6 Funding

The RAPID-PROTECTION trial is being funded by AstraZeneca and is part of the NIHR Portfolio.

21.6.1 Compensation

Participants will be compensated for their travel expenses, time and the inconvenience of having blood tests and procedures. The total amount compensated will be approximately £360 depending on the number of visits. They will be compensated £30 for attending each of the scheduled trial visits as outlined in Section 13. Should a participant decide to withdraw from the trial before it is completed, payment will be pro rata. Total costs to be invoiced by the site to Cardiff University. Participants to claim monies through the site.

22 Trial management

22.1 TMG (Trial Management Group)

The Trial Management Group (TMG) will be responsible for the day-to-day running of the trial and will meet at least once every 3 weeks in the first instance. The frequency of this will be reduced following trial opening. The TMG members will include at least the Chief Investigator, other active trial investigators, CTR Trial Statistician and CTR Trial Manager. It will also include at least one consumer representative.

The Committee's terms of reference, roles and responsibilities will be defined in a charter. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

22.2 TSC (Trial Steering Committee)

The TSC will be a committee of independent members providing overall supervision of the trial. The role of the TSC is to act on behalf of the Sponsor, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent chairperson. The TSC will review the recommendations from the IDMC and will decide on continuing or stopping the trial or modifying the protocol as required. It will meet at least annually when it will consider each report of the IDMC as well new information which has arisen and recommend appropriate action.

The Committee's terms of reference, roles and responsibilities will be defined in a charter. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

22.3 IDMC (Independent Data Monitoring Committee)

The trial data will be reviewed by an Independent Data Monitoring Committee (IDMC), consisting of at least two Clinicians (not entering patients into the trial) and an independent Statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of Clinicians including PIs in the trial and the general clinical community. The IDMC will make confidential recommendations to the Trial Steering Committee (TSC).

IDMC members will be required to sign up to the remit and conditions as set out in the DMC Charter.

23 Quality Control and Assurance

23.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the RAPID-PROTECTION trial. Moderate monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

23.2 Audits & inspections

The trial is participant to inspection by MHRA as the regulatory body. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

The site must inform the CTR of any MHRA inspections.

24 Publication policy

Ensure the information centre is acknowledged as per the data sharing agreement for any publication using NHS Digital (or any other information centre) data if required.

All publications and presentations relating to the trial will be authorised by the Trial Management Group.

A publication plan will be written. All publications and presentations relating to the trial will be authorised by the TMG.

Data from all sites will be analysed together and published as soon as possible. Individual participating PIs may not publish data concerning their participants that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will form the basis of the writing committee and advice on the nature of publications, subject to the Sponsor's requirements.

The main trial results will be published in the name of the trial in a peer-reviewed journal on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the TMG, and this may also include high accruing clinicians and/or other people who contribute to the trial. All participating centres and clinicians will be acknowledged in this main publication together with appropriate staff from the CTR.

All publications should include a list of participating PIs, and if there are named authors, these should include the CI, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial, as agreed by the CI and Director of CTR. If there are no named authors, a writing committee will be identified.

25 References

Addeo A, Shah PK, Bordry N, et al. Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. *Cancer Cell*. 2021;39(8):1091-1098.e2. doi:10.1016/j.ccell.2021.06.009Al-Janabi A, Littlewood Z, Griffiths CEM, et al. Antibody responses to single-dose SARS-CoV-2 vaccination in patients receiving immunomodulators for immune-mediated inflammatory disease. Br J Dermatol 2021; published online May 12. https://doi. org/10.1111/bjd.20479.

Avouac J, Drumez E, Hachulla E, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. *Lancet Rheumatol*. 2021;3(6):e419-e426. doi:10.1016/S2665-9913(21)00059-X

Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389Bonelli MM, Mrak D, Perkmann T, Haslacher H, Aletaha D. SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response. *Ann Rheum Dis*. 2021;80(10):1355-1356. doi:10.1136/annrheumdis-2021-220408

Blanchette PS, Chung H, Pritchard KI, et al. Influenza Vaccine Effectiveness Among Patients With Cancer: A Population-Based Study Using Health Administrative and Laboratory Testing Data From Ontario, Canada. *J Clin Oncol*. 2019;37(30):2795-2804. doi:10.1200/JCO.19.00354

Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. *JAMA*. 2021;325(17):1784-1786. doi:10.1001/jama.2021.4385

Caballero-Marcos A, Salcedo M, Alonso-Fernández R, et al. Changes in humoral immune response after SARS-CoV-2 infection in liver transplant recipients compared to immunocompetent patients. *Am J Transplant*. 2021;21(8):2876-2884. doi:10.1111/ajt.16599

Caillard S, Chavarot N, Bertrand D, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. *Kidney Int*. 2021;100(2):477-479. doi:10.1016/j.kint.2021.05.011

Carr EJ, Wu M, Harvey R, et al. Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients [published correction appears in Lancet. 2021 Aug 17]. *Lancet*. 2021;398(10305):1038-1041. doi:10.1016/S0140-6736(21)01854-7

Chen RE, Winkler ES, Case JB, Aziati ID, Bricker TL, Joshi A et al. In vivo monoclonal antibody efficacy against SARS-CoV-2 variant strains. Nature. 2021a

Deepak P, Kim W, Paley MA, et al. Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. Preprint. *medRxiv*. 2021;2021.04.05.21254656. Published 2021 Apr 9. doi:10.1101/2021.04.05.21254656

Dejnirattisai W, Zhou D, Supasa P, Liu C, Mentzer AJ, Ginn HM et al. Antibody evasion by the Brazilian P.1 strain of SARS-CoV-2. bioRxiv preprint. 2021. https://www.biorxiv.org/content/10.1101/2021.12.03.471045v2

Dejnirattisai W, Huo J, Zhou D, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. Cell. 2022;185(3):467-484.e15. doi:10.1016/j.cell.2021.12.046

Dejnirattisai W, Huo J, Zhou D, Zahradník, Supasa P, Liu C, et al, bioRxiv preprint. 2021https://www.biorxiv.org/content/10.1101/2021.12.03.471045v2

Domachowske JB, Khan AA, Esser MT, et al. Safety, Tolerability and Pharmacokinetics of MEDI8897, an Extended Half-life Single-dose Respiratory Syncytial Virus Prefusion F-targeting Monoclonal Antibody Administered as a Single Dose to Healthy Preterm Infants. *Pediatr Infect Dis J*. 2018;37(9):886-892. doi:10.1097/INF.0000000000001916

Dong J, Zost S, Greaney A, et al. Genetic and structural basis for recognition of SARS-CoV-2 spike protein by a two-antibody cocktail. Preprint. *bioRxiv*. 2021;2021.01.27.428529. Published 2021 Mar 1. doi:10.1101/2021.01.27.428529

Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet*. 2021;397(10282):1351-1362. doi:10.1016/S0140-6736(21)00628-0

van Erp EA, Luytjes W, Ferwerda G, van Kasteren PB. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. *Front Immunol*. 2019;10:548. Published 2019 Mar 22. doi:10.3389/fimmu.2019.00548

Flaxman A, Marchevsky NG, Jenkin D, et al. Tolerability and Immunogenicity After a Late Second Dose or a Third Dose of ChAdOx1 nCoV-19 (AZD1222). *Lancet* 2021; 398(10304): 981-990. doi: 10.1016/S0140-6736(21)01699-8

Gram M A, Nielsen J, Schelde AB, et al. Vaccine effectiveness when combining the ChAdOx1 vaccine as the first dose with an mRNA COVID-19 vaccine as the second dose. Pre-print: medRxiv 2021.07.26.21261130; doi: https://doi.org/10.1101/2021.07.26.21261130

Griffin MP, Khan AA, Esser MT, et al. Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults. *Antimicrob Agents Chemother*. 2017;61(3):e01714-16. Published 2017 Feb 23. doi:10.1128/AAC.01714-16

Haberman RH, Herati RS, Simon D, et al. Methotrexate Hampers Immunogenicity to BNT162b2 mRNA COVID-19 Vaccine in Immune-Mediated Inflammatory Disease. Preprint. *medRxiv*. 2021;2021.05.11.21256917. Published 2021 May 12. doi:10.1101/2021.05.11.21256917

Hall VG, Ferreira VH, Ku T, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients [published online ahead of print, 2021 Aug 11]. *N Engl J Med*. 2021;NEJMc2111462. doi:10.1056/NEJMc2111462

Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-3173. doi:10.1182/blood.2021011568

Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave [published online ahead of print, 2022 Jun 21]. Am J Transplant. 2022;10.1111/ajt.17128. doi:10.1111/ajt.17128

Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *N Engl J Med*. 2021;385(7):661-662. doi:10.1056/NEJMc2108861

Kearns P, Siebert S, Willicombe M, et al. Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacity – The OCTAVE Trial. [preprint]Available at SSRN: https://ssrn.com/abstract=3910058 or http://dx.doi.org/10.2139/ssrn.3910058

Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut*. 2021;70(10):1884-1893. doi:10.1136/gutjnl-2021-324789

Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(7):1205-1211. doi:10.1038/s41591-021-01377-8

Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study [published correction appears in Lancet. 2020 Sep 12;396(10253):758]. *Lancet*. 2020;395(10241):1907-1918. doi:10.1016/S0140-6736(20)31187-9

Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study [published correction appears in Lancet. 2020 Aug 22;396(10250):534]. *Lancet*. 2020;395(10241):1919-1926. doi:10.1016/S0140-6736(20)31173-9

Lesny P, Anderson M, Cloherty G, et al. Immunogenicity of a first dose of mRNA- or vector-based SARS-CoV-2 vaccination in dialysis patients: a multicenter prospective observational pilot study. *J Nephrol*. 2021;34(4):975-983. doi:10.1007/s40620-021-01076-0

Loo, Yueh-Ming, McTamney, Patrick M, Arends, Rosalinda H, Gasser, Robert A, Abram, Michael E, et al, https://www.medrxiv.org/content/10.1101/2021.08.30.21262666v2.

Liu C, Ginn HM, Dejnirattisai W, et al. Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. *Cell*. 2021;184(16):4220-4236.e13. doi:10.1016/j.cell.2021.06.020

Liu X, Shaw RH, Stuart ASV, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. *Lancet*. 2021;398(10303):856-869. doi:10.1016/S0140-6736(21)01694-9

Lusvarghi S, Wang W, Herrup R, Neerukonda SN, Vassell R, Bentley L et al. Key substitutions in the spike protein of SARS-CoV-2 variants can predict resistance to monoclonal antibodies, but other substitutions can modify the effects. bioRxiv preprint. 2021.

Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study [published correction appears in Lancet Oncol. 2021 Jan;22(1):e5]. *Lancet Oncol*. 2020;21(8):1023-1034. doi:10.1016/S1470-2045(20)30388-0

Monin-Aldama L, Laing A G, Muñoz-Ruiz M, et al. Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines. medRxiv 2021.03.17.21253131; doi: https://doi.org/10.1101/2021.03.17.21253131

Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, Kim K, Campos JAS, Arends RH, Brodek BH, Brooks D, Garbes P, Jimenez J, Koh GCKW, Padilla KW, Streicher K, Viani RM, Alagappan V, Pangalos MN, Esser MT; TACKLE study group. Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2022 Jun 7:S2213-2600(22)00180-1. doi: 10.1016/S2213-2600(22)00180-1. Epub ahead of print. PMID: 35688164; PMCID: PMC9173721.

National Institutes of Health. National Center for Advancing Translational Sciences Open Data Portal. SARS-CoV-2 Variants & Therapeutics. AZD7442 (AZD8895 and AZD1061; mAbs for SARS-CoV-2) Omicron Antiviral Resistance Information. Available at: https://opendata.ncats.nih.gov/variant/datasets?id=160 [Last accessed February 2022].

Nordström P, Ballin M, Nordström A. Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: A nationwide cohort study. Lancet Reg Health Eur. 2021;11:100249. doi:10.1016/j.lanepe.2021.100249

Nugent C, Guo W, Müller P, Ji Y. Bayesian Approaches to Subgroup Analysis and Related Adaptive Clinical Trial Designs. *JCO Precis Oncol*. 2019;3:PO.19.00003. Published 2019 Oct 24. doi:10.1200/PO.19.00003

Parry H, Bruton R, Tut G, et al. Immunogenicity of single vaccination with BNT162b2 or ChAdOx1 nCoV-19 at 5-6 weeks post vaccine in participants aged 80 years or older: an exploratory analysis. *Lancet Healthy Longev*. 2021;2(9):e554-e560. doi:10.1016/S2666-7568(21)00169-0

Perry C, Luttwak E, Balaban R, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. *Blood Adv*. 2021;5(16):3053-3061. doi:10.1182/bloodadvances.2021005094

Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

Pozzetto B, Legros V, Djebali S, et al. Immunogenicity and efficacy of heterologous ChAdOx1-BNT162b2 vaccination [published online ahead of print, 2021 Oct 21]. Nature. 2021;10.1038/s41586-021-04120-y. doi:10.1038/s41586-021-04120-y

Pouwels K B, Pritchard E, Matthews P C, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. [Pre-print]; copy https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/finalfinalcombinedve20210816.pdf

Prendecki M, Thomson T, Clarke C L, et al. Comparison of humoral and cellular responses in kidney transplant recipients receiving BNT162b2 and ChAdOx1 SARS-CoV-2 vaccines. [Preprint] medRxiv 2021.07.09.21260192; doi: https://doi.org/10.1101/2021.07.09.21260192

Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial [published correction appears in Lancet. 2021 Dec 19;396(10267):1978] [published correction appears in Lancet. 2021 Apr 10;397(10282):1350]. *Lancet*. 2021;396(10267):1979-1993. doi:10.1016/S0140-6736(20)32466-1

Robbie GJ, Criste R, Dall'acqua WF, et al. A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE, has an extended half-life in healthy adults. *Antimicrob Agents Chemother*. 2013;57(12):6147-6153. doi:10.1128/AAC.01285-13

Redchenko Irina, Cappuccini F, Pollock P, et al. "VANCE: First-in-human Phase I Study of a Novel ChAdOx1-MVA 5T4 Vaccine in Low and Intermediate Risk Prostate Cancer." Journal Of Clinical Oncology 36.15 (2018): 3018-3018.

Sabino EC, Buss LF, Carvalho MPS, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. *Lancet*. 2021;397(10273):452-455. doi:10.1016/S0140-6736(21)00183-5

Salviani C, Scolari F, Alberici F. Correspondence on 'Immunogenicity and safety of anti-SARS-Cov-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'. *Ann Rheum Dis*. 2021;80(10):e158. doi:10.1136/annrheumdis-2021-220496

Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study [published correction appears in Lancet Haematol. 2021 Jun;8(6):e393]. *Lancet Haematol*. 2021;8(3):e185-e193. doi:10.1016/S2352-3026(20)30429-4

Simon B, Rubey H, Treipl A, et al. Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared with healthy controls. *Nephrol Dial Transplant*. 2021;36(9):1709-1716. doi:10.1093/ndt/gfab179

Simon D, Tascilar K, Fagni F, et al. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis*. 2021;80(10):1312-1316. doi:10.1136/annrheumdis-2021-220461

Simon D, Tascilar K, Schmidt K, et al. Brief Report: Humoral and cellular immune responses to SARS-CoV-2 infection and vaccination in B cell depleted autoimmune patients [published online ahead of print, 2021 Jul 1]. *Arthritis Rheumatol*. 2021;10.1002/art.41914. doi:10.1002/art.41914

Schmidt T, Klemis V, Schub D, et al. Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector-based COVID-19 vaccine regimens in solid organ transplant recipients. Am J Transplant. 2021;21(12):3990-4002. doi:10.1111/ajt.16818

Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis*. 2021;80(10):1357-1359. doi:10.1136/annrheumdis-2021-220604

Tau N, Yahav D, Schneider S, Rozen-Zvi B, Abu Sneineh M, Rahamimov R. Severe consequences of COVID-19 infection among vaccinated kidney transplant recipients. *Am J Transplant*. 2021;21(8):2910-2912. doi:10.1111/ajt.16700

Thakkar, A., Pradhan, K., Jindal, S. *et al.* Patterns of seroconversion for SARS-CoV-2 IgG in patients with malignant disease and association with anticancer therapy. *Nat Cancer* **2,** 392–399 (2021). https://doi.org/10.1038/s43018-021-00191-y

Tuekprakhon, A., Nutalai, R., Dijokaite-Guraliuc, A., Zhou, D., Ginn, H. M., Selvaraj, M., Liu, C., Mentzer, A. J., Supasa, P., Duyvesteyn, H., Das, R., Skelly, D., Ritter, T. G., Amini, A., Bibi, S., Adele, S., Johnson, S. A., Constantinides, B., Webster, H., Temperton, N., … Screaton, G. R. (2022). Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. Cell, 185(14), 2422–2433.e13. https://doi.org/10.1016/j.cell.2022.06.005

US Food and Drug Administration FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELDTM (Tixagevimab Co-Packaged with Cilgavimab). Available at: https://www.fda.gov/media/154701/download [Last accessed: July 2022]

VanBlargan LA, Errico JM, Halfmann PJ, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. Nat Med. 2022;28(3):490-495. doi:10.1038/s41591-021-01678-y

Van Oekelen O, Gleason CR, Agte S, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell. 2021;39(8):1028-1030. doi:10.1016/j.ccell.2021.06.014

Vasileiou E, Simpson C, Robertson, C, Shi T, et al: Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People: [preprint] https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264

Vector Engineering Lab et al. COVID CG. https://covidcg.org/ [Last accessed: July 2022]

Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK [published correction appears in Lancet. 2021 Jan 9;397(10269):98]. *Lancet*. 2021;397(10269):99-111. doi:10.1016/S0140-6736(20)32661-1

Wang et al 2021a : Wang P, Casner RG, Nair MS, Wang M, Yu J, Cerutti G et al. Increased resistance of SARSCoV-2 variant P.1 to antibody neutralization. Cell Host Microbe. 2021a;29(5):747-51 e4.

Wang et al 2021b : Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature. 2021b;593(7857):130-5

Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Ann Intern Med*. 2021;174(9):1330-1332. doi:10.7326/L21-0282

Young-Xu Y, Epstein L, Marconi V, Davey V, Zwain G, Smith J, Korves C, Cunningham F, Bonomo R, Ginde A A. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data. medRxiv 2022.05.28.22275716; doi: https://doi.org/10.1101/2022.05.28.22275716

Yu XQ, Robbie GJ, Wu Y, et al. Safety, Tolerability, and Pharmacokinetics of MEDI4893, an Investigational, Extended-Half-Life, Anti-Staphylococcus aureus Alpha-Toxin Human Monoclonal Antibody, in Healthy Adults. *Antimicrob Agents Chemother*. 2016;61(1):e01020-16. Published 2016 Dec 27. doi:10.1128/AAC.01020-16

Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. doi:10.1056/NEJMoa2001017

Zhou D, Dejnirattisai W, Supasa P, Liu C, Mentzer AJ, Ginn HM et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell. 2021;184(9):2348-61.

Zost SJ, Gilchuk P, Case JB, et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature*. 2020;584(7821):443-449. doi:10.1038/s41586-020-2548-6

Other reference material

Department of Health and Social Care, 1st September 2021. Joint Committee on Vaccination and Immunisation (JCVI) advice on third primary dose vaccination. https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-

who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination#fn:5

26 Appendices

APPENDIX 1: High priority for a third vaccine doses by the Joint Committee on Vaccination and Immunisation (JCVI)

Individuals on immunosuppressive or immunomodulating therapy at the time of vaccination

- acute and chronic leukaemia's and clinically aggressive lymphomas (including Hodgkin's lymphoma) who were under treatment or within 12 months of achieving cure
- individuals under follow up for chronic lymphoproliferative disorders including haematological malignancies such as indolent lymphoma, chronic lymphoid leukaemia, myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias (note: this list is not exhaustive)
- immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/µl for adults or children
- primary or acquired cellular and combined immune deficiencies – those with lymphopenia (<1,000 lymphocytes/ul) or with a functional lymphocyte disorder
- those who had received an allogeneic (cells from a donor) or an autologous (using their own cells) stem cell transplant in the previous 24 months
- those who had received a stem cell transplant more than 24 months ago but had ongoing immunosuppression or graft versus host disease (GVHD)
- persistent agammaglobulinaemia (IgG < 3g/L) due to primary immunodeficiency (for example, common variable immunodeficiency) or secondary to disease/therapy

Individuals with primary or acquired immunodeficiency states at the time of vaccination

- those who were receiving or had received immunosuppressive therapy for a solid organ transplant in the previous 6 months
- those who were receiving or had received in the previous 3 months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but in this case the recipient would be considered immunosuppressed for a 6-month period), T-cell co-stimulation modulators, monoclonal tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors (note: this list is not exhaustive)
- those who were receiving or had received in the previous 6 months immunosuppressive chemotherapy or radiotherapy for any indication

Individuals with chronic immune-mediated inflammatory disease who were receiving or had received immunosuppressive therapy prior to vaccination

- high-dose corticosteroids (equivalent to ≥ 20mg prednisolone per day) for more than 10 days in the previous month
- long-term moderate dose corticosteroids (equivalent to ≥10mg prednisolone per day for more than 4 weeks) in the previous 3 months

- non-biological oral immune modulating drugs, such as methotrexate >20mg per week (oral and subcutaneous), azathioprine >3.0mg/kg/day, 6-mercaptopurine >1.5mg/kg/day, mycophenolate >1g/day in the previous 3 months
- certain combination therapies at individual doses lower than above, including those on ≥7.5mg prednisolone per day in combination with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) and those receiving methotrexate (any dose) with leflunomide in the previous 3 months

Individuals who had received high-dose steroids for any reason in the month before vaccination.

APPENDIX 2 - WHO Clinical Progression Scale

Patient State	**Descriptor**	**Score**
Uninfected	Uninfected; no viral RNA detected.	0
Ambulatory mild disease	Asymptomatic; viral RNA detected Symptomatic; independent Symptomatic; assistance needed	1 2 3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy* Hospitalised; oxygen by mask or nasal prongs	4 5
Hospitalised: Severe disease	Hospitalised; oxygen by NIV or high flow Intubation and mechanical ventilation, pO_2/FiO_2 150 or SpO_2/FiO_2 200 Mechanical ventilation $pO_2/FiO_2 <$ 150 ($SpO_2/FiO_2 <$ 200) or vasopressors Mechanical ventilation $pO_2/FiO_2 <$ 150 and vasopressors, dialysis, or ECMO	6 7 8 9
Dead	Dead	10

*ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2=partial pressure of oxygen. SpO_2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.*

APPENDIX 3 - Current International Classification of Diseases for Oncology (ICD-O-3) codes for haematological cancers and related precursor conditions. These new codes were approved by the IARC/WHO Committee for ICD-O.

These codes take the format '1234/1' with the first four numbers representing the cell or tumour type and the final number representing the behaviour, ranging from 0 to 3. Behaviour codes are defined as: /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for carcinoma in situ, /3 for malignant tumours.

	ICD-O-3 codes
Myeloproliferative neoplasms	9875/3, 9950/3, 9961/3, 9962/3, 9975/3
Chronic myeloid leukaemia	9875/3
Myelofibrosis	9961/3
Polycythaemia vera	9950/3
Essential thrombocythaemia	9962/3
Myeloproliferative neoplasm, unclassifiable	9975/3
Myelodysplastic / Myeloproliferative neoplasms	9876/3, 9945/3, 9946/3, 9975/3, 9982/3
Chronic myelomonocytic leukaemia	9945/3
Juvenile chronic myelomonocytic leukaemia	9946/3
Atypical chronic myeloid leukaemia	9876/3
Myelodysplastic / myeloproliferative neoplasm unclassified	9975/3
MDS/MPN with ring sideroblasts and thrombocytosis	9982/3
Myelodysplastic syndromes	9920/3, 9982/3, 9983/3, 9985/3, 9986/3, 9989/3, 9993/3*
MDS with ring sideroblasts	9982/3, 9993/3*
MDS with multilineage dysplasia	9985/3
MDS with excess blasts	9983/3
MDS with isolated del(5q)	9986/3
Myelodysplastic syndrome, unclassifiable	9989/3
Therapy related MDS	9920/3
Acute myeloid leukaemias	9861/3, 9865/3, 9866/3, 9869/3, 9871/3, 9877/3*, 9878/3*, 9879/3*, 9895/3, 9896/3, 9897/3, 9920/3
Acute myeloid leukaemia	9861/3, 9865/3, 9869/3, 9871/3, 9877/3*, 9878/3*, 9879/3*, 9895/3, 9896/3, 9897/3, 9920/3

Acute myeloid leukaemia, NOS	9861/3
AML with recurrent genetic abnormalities	9865/3, 9869/3, 9871/3, 9877/3*, 9878/3*, 9879/3*, 9896/3, 9897/3
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1	9896/3
AML with inv(16)(p13.1;1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	9871/3
AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3	9897/3
AML with t(6;9)(p23;q34.1); DEK-NUP214	9865/3
AML with inv3(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	9869/3
AML with mutated NPM1	9877/3*
AML with biallelic mutation of CEBPA	9878/3*
AML with mutated RUNX1	9879/3*
AML with myelodysplasia-related changes	9895/3
Therapy related AML	9920/3
Acute promyelocytic leukaemia	9866/3
Acute lymphoblastic leukaemia	9811/3, 9812/3, 9813/3, 9814/3, 9815/3, 9816/3, 9818/3, 9819/3*, 9837/3
B-lymphoblastic leukaemia	9811/3, 9812/3, 9813/3, 9814/3, 9815/3, 9816/3, 9818/3, 9819/3*
B-lymphoblastic leukaemia / lymphoma, NOS	9811/3
B-lymphoblastic leukaemia / lymphoma with t(9,22)(q34.1;q11.2); BCR-ABL1	9812/3
B-lymphoblastic leukaemia / lymphoma with t(v11q23.3); KMT2A-rearranged	9813/3
B-lymphoblastic leukaemia / lymphoma with t(12;21)(p13.2;q22.1); ETV-RUNX1	9814/3
B-lymphoblastic leukaemia / lymphoma with hyperdiploidy	9815/3
B-lymphoblastic leukaemia / lymphoma with hypodiploidy	9816/3
B-lymphoblastic leukaemia / lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1	9818/3
B-lymphoblastic leukaemia / lymphoma, BCR-ABL1-like	9819/3*

B-lymphoblastic leukaemia / lymphoma with iAMP21	9811/3
T-lymphoblastic leukaemia	T-lymphoblastic leukaemia / lymphoma (9837/3), Early T-cell precursor lymphoblastic leukaemia (9837/3)
Mature B-cell neoplasms	9579/3, 9591/3, 9673/3, 9679/3, 9680/3, 9687/3, 9688/3, 9689/3, 9690/3, 9695/3, 9698/3, 9699/3, 9712/3, 9731/3, 9732/3, 9734/3, 9735/3, 9765/1, 9769/1, 9823/1, 9823/3, 9940/3
Monoclonal B-cell lymphocytosis	9823/1
Chronic lymphocytic leukaemia	9823/3
Hairy cell leukaemia	9940/3
Lymphoproliferative disorders, NOS	9591/3, 9823/3
Marginal zone lymphoma	9689/3, 9699/3
Monoclonal gammopathy of undetermined significance	9765/1
Plasma cell neoplasms	9731/3, 9732/3, 9734/3, 9769/1
Plasmacytoma	9731/3, 9734/3
Solitary plasmacytoma of bone	9731/3
Extraosseous plasmacytoma	9734/3
Myeloma	9732/3
Follicular lymphoma	9579/3, 9690/3, 9695/3, 9698/3
Follicular lymphoma, NOS	9690/3
Follicular lymphoma; large cell	9698/3
Duodenal-type follicular lymphoma	9695/3
Primary cutaneous follicle centre lymphoma	9579/3
Mantle cell lymphoma	9673/3
Large B-cell lymphomas	9679/3, 9680/3, 9688/3, 9698/3, 9712/3, 9735/3
Large B-cell lymphoma with IRF4 rearrangement	9698/3
Diffuse large B-cell lymphoma (DLBCL), NOS	Diffuse large B-cell lymphoma (DLBCL), NOS (9680/3), High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements (9680/3), High grade B-cell lymphoma, NOS (9680/3)
T-cell/histiocyte-rich large B-cell lymphoma	9688/3

Primary diffuse large B-cell lymphoma of the CNS	9680/3
Primary cutaneous DLBCL, leg type	9680/3
Primary mediastinal large B-cell lymphoma	9679/3
Intravascular large B-cell lymphoma	9712/3
Plasmablastic lymphoma	9735/3
Burkitt lymphoma	9687/3
Mature T- and NK-cell neoplasms	9700/3, 9701/3, 9702/3, 9705/3, 9709/3, 9714/3, 9716/3, 9717/3, 9718/3, 9719/3, 9726/3, 9827/3, 9831/3, 9834/3
Peripheral T-cell lymphomas	9702/3, 9705/3, 9714/3, 9716/3, 9717/3, 9719/3, 9827/3
Peripheral T-cell lymphoma, NOS	9702/3
Extranodal NK/T-cell lymphoma, nasal type	9719/3
Intestinal T-cell lymphoma	9717/3
Hepatosplenic T-cell lymphoma	9716/3
Adult T-cell leukaemia/lymphoma	9827/3
Angioimmunoblastic T-cell lymphoma	9705/3
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
Cutaneous T-cell lymphomas	9700/3, 9701/3, 9709/3, 9718/3, 9726/3
Mycosis fungoides	9700/3
Sezary syndrome	9701/3
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	9718/3
Primary cutaneous gamma delta T-cell lymphoma	9726/3
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
T-cell prolymphocytic leukaemia	9834/3
T-cell large granular lymphocytic leukaemia	9831/3
Hodgkin lymphoma	9650/3, 9651/3, 9652/3, 9653/3, 9659/3, 9663/3
Classical Hodgkin lymphoma	Classical Hodgkin lymphoma (9650/3), Classical Hodgkin lymphoma - Lymphocyte-depleted (9653/3), Classical Hodgkin lymphoma - lymphocyte rich (9651/3), Classical Hodgkin lymphoma - mixed

	cellularity (9652/3), Classical Hodgkin lymphoma - nodular sclerosing type (9663/3)
Nodular lymphocyte predominant Hodgkin lymphoma	9659/3

** These new codes were approved by the IARC/WHO Committee for ICD-O.*