UNIVERSITY OF BIRMINGHAM

Immunogenicity and safety of AZD2816, a beta (B.1.351) variant COVID-19 vaccine, and AZD1222 (ChAdOx1 nCoV-19) as third-dose boosters for previously vaccinated adults

AZD2816 Study Group; Ramasamy, Maheshi N; Kelly, Elizabeth J.; Seegobin, Seth; Dargan, Paul I; Payne, Ruth; Libri, Vincenzo; Adam, Matthew; Aley, Parvinder K; Martinez-Alier, Nuria; Church, Alison; Jepson, Brett; Khan, Mark; Matthews, Sam; Townsend, G Todd; Vekemans, Johan; Bibi, Sagida; Swanson, Phillip A; Lambe, Teresa; Pangalos, Menelas N

Link to publication on Research at Birmingham portal

Immunogenicity and safety of AZD2816, a beta (B.1.351) variant COVID-19 vaccine, and AZD1222 (ChAdOx1 nCoV-19) as third-dose boosters for previously vaccinated adults: a multicentre, randomised, partly double-blinded, phase 2/3 non-inferiority immunobridging study in the UK and Poland

Maheshi N Ramasamy*, Elizabeth J Kelly*, Seth Seegobin*, Paul I Dargan, Ruth Payne, Vincenzo Libri, Matthew Adam, Parvinder K Aley, Nuria Martinez-Alier, Alison Church, Brett Jepson, Mark Khan, Sam Matthews, G Todd Townsend, Johan Vekemans, Sagida Bibi, Phillip A Swanson II, Teresa Lambe, Menelas N Pangalos, Tonya Villafana, Andrew J Pollard†, Justin A Green†, and the AZD2816 Study Group‡

Summary

Background This study aimed to evaluate AZD2816, a variant-updated COVID-19 vaccine expressing the full-length SARS-CoV-2 beta (B.1.351) variant spike protein that is otherwise similar to AZD1222 (ChAdOx1 nCoV-19), and AZD1222 as third-dose boosters.

Methods This phase 2/3, partly double-blinded, randomised, active-controlled study was done at 19 sites in the UK and four in Poland. Adult participants who had received a two-dose AZD1222 or mRNA vaccine primary series were randomly assigned by means of an Interactive Response Technology–Randomisation and Trial Supply Management system (1:1 within each primary-series cohort, stratified by age, sex, and comorbidities) to receive AZD1222 or AZD2816 (intramuscular injection; 5×10^{10} viral particles). Participants, investigators, and all sponsor staff members involved in study conduct were masked to randomisation. AZD1222 and AZD2816 doses were prepared by unmasked study staff members. The primary objectives were to evaluate safety and humoral immunogenicity (non-inferiority of day-29 pseudovirus neutralising antibody geometric mean titre [GMT] against ancestral SARS-CoV-2: AZD1222 booster *vs* AZD1222 primary series [historical controls]; margin 0·67; SARS-CoV-2-seronegative participants). This study is registered with ClinicalTrials.gov, NCT04973449, and is completed.

Findings Between June 27 and Sept 30, 2021, 1394 participants of the 1741 screened were randomly assigned to AZD1222 or AZD2816 following an AZD1222 (n=373, n=377) or mRNA vaccine (n=322, n=322) primary series. In SARS-CoV-2-seronegative participants receiving AZD1222 or AZD2816, 78% and 80% (AZD1222 primary series) and 90% and 93%, respectively (mRNA vaccine primary series) reported solicited adverse events to the end of day 8; 2%, 2%, 1%, and 1% had serious adverse events and 12%, 12%, 10%, and 11% had adverse events of special interest, respectively, to the end of day 180. The primary immunogenicity non-inferiority endpoint was met: day-29 neutralising antibody GMT ratios (ancestral SARS-CoV-2) were 1·02 (95% CI 0·90–1·14) and 3·47 (3·09–3·89) with AZD1222 booster versus historical controls (AZD1222 and mRNA vaccine primary series, respectively). Responses against beta were greater with AZD2816 versus AZD1222 (GMT ratios, AZD1222, mRNA vaccine primary series 1·84 [1·63–2·08], 2·22 [1·99–2·47]).

Interpretation Both boosters were well tolerated, with immunogenicity against ancestral SARS-CoV-2 similar to AZD1222 primary-series vaccination. AZD2816 gave greater immune responses against beta versus AZD1222.

Funding AstraZeneca.

Introduction

COVID-19 vaccines developed against ancestral SARS-CoV-2 have provided highly effective population-level protection and substantially prevented severe disease, hospitalisation, and death caused by COVID-19.[1,2] However, SARS-CoV-2 variants of concern continue to emerge; these variants have shown increased transmissibility and some immune evasion, and have resulted in decreased vaccine effectiveness.[3] Although mortality rate has been reduced, owing largely to protection provided by existing vaccination strategies,[1] COVID-19 remains a leading health issue in populations at increased risk of hospitalisation and death from respiratory infections, such as immunocompromised individuals, older adults with comorbidities, and other vulnerable populations.[2]

and Formerly Paediatric
Infectious Diseases and
Immunology, Evelina London
Children's Hospital
(N Martinez-Alier MD), Guy's
and St Thomas' NHS
Foundation Trust, London, UK;
Faculty of Life Sciences and
Medicine, King's College
London, London, UK
(P I Dargan); Department of
Infection, Immunity and
Cardiovascular Disease, The
Medical School, University of
Sheffield, Sheffield, UK
(R Payne PhD); Sheffield
Teaching Hospitals NHS
Foundation Trust, Sheffield, UK
(R Payne); National Institute for
Health and Care Research,
University College London
Hospitals, Clinical Research
Facility, London, UK
(V Libri MD); National Institute
for Health and Care Research,
University College London
Hospitals, Biomedical Research
Centre, London, UK (V Libri);
Clinical Infection Research
Group—Edinburgh, Regional
Infectious Diseases Unit, NHS
Lothian, Edinburgh, UK
(M Adam MB BChir); IQVIA,
London, UK (N Martinez-Alier);
Clinical Development, Vaccines
and Immune Therapies,
BioPharmaceuticals R&D,
AstraZeneca, Durham, NC, USA
(A Church MD); Clinical
Development,
BioPharmaceuticals R&D,
AstraZeneca, Mississauga, ON,
Canada (M Khan BS); Clinical
Development, Vaccines and
Immune Therapies,
BioPharmaceuticals R&D,
AstraZeneca, Gothenburg,
Sweden (G T Townsend PhD);
Oxford Vaccine Group, Centre
for Clinical Vaccinology and
Tropical Medicine, Churchill
Hospital, Oxford, UK
(T Lambe PhD); Chinese
Academy of Medical Science
Oxford Institute, University of
Oxford, Oxford, UK (T Lambe)

Correspondence to:
Dr Justin A Green, Clinical
Development, Vaccines and
Immune Therapies,
BioPharmaceuticals R&D,
AstraZeneca,
Cambridge CB2 8DU, UK
justin.green@astrazeneca.com

See Online for appendix

Research in context

Evidence before this study

We did a literature search via PubMed for research articles published from December, 2020 until September, 2022 using the search terms "COVID-19", "vaccine", and "booster"; before the start of this study, there were no published papers on the use of AZD1222 as a third-dose booster or on the use of AZD2816 in humans. The published literature shows that booster dosing strategies that make use of approved COVID-19 vaccines have helped maintain the high levels of protection against hospitalisation and death in vulnerable individuals that were established with primary-series vaccination programmes. This is consistent with the substantial immunogenicity shown in studies examining both homologous and heterologous boosting approaches such as the UK phase 2 COV-BOOST trial. With the emergence of SARS-CoV-2 variants that are more transmissible and more able to evade the primary humoral immune response, regulatory authorities have indicated the need to update these original vaccines, which were developed against ancestral SARS-CoV-2, with the aim of enhancing the magnitude, duration, and breadth of immunity conferred by vaccination and reducing infection rates in those with comorbidities or frailty at highest risk of hospitalisation. Variant-updated and bivalent booster vaccine approaches offer potential solutions, and immunobridging studies of these novel vaccines—as well as of existing vaccines—can be used to indicate probable vaccine efficacy of boosters through comparisons of immune responses with levels of immunity achieved following a primary series with known efficacy.

Added value of this study

This analysis reports the first clinical data on a variant-updated COVID-19 vaccine developed with the ChAdOx1 platform used for AZD1222 (ChAdOx1 nCoV-19). AZD2816 expresses the full-length spike protein from the SARS-CoV-2 beta (B.1.351)

variant of concern. This study evaluates the immunogenicity of AZD1222 and AZD2816 as third-dose boosters after a primary series of either AZD1222 or an mRNA vaccine against both ancestral SARS-CoV-2 and beta, as well as against the delta (B.1.617.2) and omicron (B.1.1.529) variants. Importantly, these findings show that an AZD1222 booster provides levels of immunogenicity similar to those measured after a two-dose primary series. This immunobridging study thus suggests that booster dosing might be sufficient to achieve the very high levels of protection against severe COVID-19 and the reduced infection rate in populations vulnerable to hospitalisation and death, when they develop COVID-19 as a cofactor with a pre-existing comorbidity, previously shown after two-dose primary-series vaccination. Our analyses also show that AZD2816 not only results in greater neutralising antibody responses against beta than an AZD1222 booster but that it also maintains the level of response against ancestral SARS-CoV-2.

Implications of all the available evidence

These findings highlight the feasibility of developing a variant-updated vaccine by use of the ChAdOx1 platform and show that AZD2816 provides enhanced targeted immune responses against the beta variant and neutralising antibody responses against ancestral SARS-CoV-2. They also highlight that AZD1222 as a third-dose booster elicits elevated immune responses against ancestral SARS-CoV-2, as well as against the beta, delta, and omicron variants, regardless of primary series, suggesting that AZD1222 remains an important option for booster dosing to prevent hospitalisation and death associated with COVID-19, particularly for low-to-middle-income countries with logistical and financial challenges associated with booster vaccine roll-out.

Homologous and heterologous booster strategies that make use of approved COVID-19 vaccines developed against ancestral SARS-CoV-2 have been widely adopted to boost humoral immune responses and maintain protection against hospitalisation and death associated with SARS-CoV-2 variants.[4–7] With the aim of enhancing the magnitude, duration, and breadth of immunity conferred and providing cross-protection against multiple variants,[2] COVID-19 vaccines with updated antigen composition have been developed.[8–11] When it emerged, the beta (B.1.351) variant was the most antigenically distinct SARS-CoV-2 variant,[12] with reduced sensitivity to vaccine-elicited antibodies; thus, variant-updated and bivalent vaccines have been developed that express the beta spike protein. More recently, bivalent mRNA vaccines against the omicron (B.1.1.529) BA.1 or BA.4/5 subvariants plus ancestral SARS-CoV-2 have been introduced in some countries' booster programmes.[8–11]

The replication-deficient simian adenovirus-vectored vaccine AZD1222 (ChAdOx1 nCoV-19), which encodes the full-length spike protein from ancestral SARS-CoV-2,[13] has been one of the most widely used COVID-19 vaccines globally.[1] In clinical trials, a two-dose AZD1222 primary series had a well tolerated safety profile and was immunogenic and highly efficacious against COVID-19 and severe disease,[14–17] showing durable protection and immunogenicity through a median follow-up of 6 months.[17] In a phase 2 trial, AZD1222 as a third-dose booster, following homologous or mRNA vaccine primary-series vaccination, showed an acceptable safety profile and enhanced humoral and cellular responses against both ancestral SARS-CoV-2 and the delta (B.1.617.2) variant.[18] Real-world studies have shown that AZD1222 is effective as a homologous or heterologous third-dose booster, providing high levels of protection against severe disease across variants.[4,7]

By use of the same platform as AZD1222, the variant-updated ChAdOx1-vectored vaccine AZD2816 has been developed to express the full-length beta spike protein.[11] In preclinical studies, an AZD2816 booster dose in animals primed with AZD1222 increased binding and pseudovirus neutralising antibodies against the beta, gamma (P.1), and delta variants.[11,19] This phase 2/3, randomised study analysed the safety and immunogenicity of AZD1222 and AZD2816 boosters in participants who had received an AZD1222 or mRNA vaccine primary series. We also evaluated the potential efficacy of AZD1222 and AZD2816 as inferred by immunobridging, using comparisons of pseudovirus neutralising antibody titres, versus a historical control cohort with known efficacy from the phase 3 trial of primary-series AZD1222.[16]

Methods

Study design and participants

This phase 2/3, partly double-blinded, randomised, multinational, active-controlled study (ClinicalTrials.gov, NCT04973449) evaluated the safety and immunogenicity of AZD1222 or AZD2816 as a single-dose booster vaccination in adults who were previously vaccinated with a two-dose primary series of AZD1222 or an mRNA vaccine. This report includes safety data and immune responses from participants enrolled at 19 sites in the UK and four sites in Poland to study completion (day 180; database lock, Sept 22, 2022). The study also includes a four-arm component evaluating primary-series AZD1222 and AZD2816 in unvaccinated participants (appendix p 27); this component will be reported elsewhere. This study was done in accordance with ethical principles originating in the Declaration of Helsinki and consistent with International Council for Harmonisation Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics. The protocol and amendments were approved by the ethics committee or institutional review board at each centre. All participants provided written informed consent.

Participants aged at least 18 years (UK protocol amendment ≥30 years) who were healthy or had stable chronic medical conditions (no significant change in therapy or hospitalisation within 90 days before enrolment) were eligible for this booster component of the study. Participants had previously completed a homologous two-dose primary vaccination series with AZD1222 (4–12-week dosing interval) or an authorised mRNA vaccine (BNT162b2, 3–12-week dosing interval; mRNA-1273, 4–12-week dosing interval), with second doses administered at least 90 days before study booster dose. Participants could be SARS-CoV-2 nucleocapsid seronegative or seropositive at baseline. For inclusion in the seronegative population for the primary and secondary objectives, participants were required to have no history of laboratory-confirmed SARS-CoV-2 infection and to be seronegative for SARS-CoV-2 nucleocapsid antibody at screening (via lateral flow test). Participants who were seropositive at screening could be enrolled (number capped at 10% of the seronegative population) in the seropositive population for analysis of exploratory objectives. Participants with any confirmed or suspected immunosuppressive or immunodeficient state (including asplenia or HIV/AIDS, recurrent severe infections, and use of immunosuppressant medication within the past 6 months), or history of thrombocytopenia or thrombosis, or both, were excluded. All eligibility criteria are provided within the protocol (appendix).

Randomisation and masking

Participants previously vaccinated with AZD1222 or an mRNA vaccine were randomly assigned in separate cohorts, in a 1:1 ratio within each cohort, to receive AZD1222 or AZD2816 (intramuscular injection; each 5×10^{10} viral particles) as a booster (appendix p 27). Randomisation was stratified by age (<65 years, ≥65 years), sex, and presence or absence of at least one of the following comorbidities: obesity (BMI ≥30 kg/m² at baseline), notable cardiovascular disease, chronic lung disease, and diabetes (appendix p 5). Participants were assigned by means of an Interactive Response Technology–Randomisation and Trial Supply Management system (appendix p 5). Treatment was double-blinded; participants, investigators, and sponsor staff members involved in study conduct were masked to randomisation. AZD1222 and AZD2816 dose preparation was done by an unmasked pharmacist or designee at each site as they had visually distinct packaging before being drawn into syringes.

Procedures

Participants attended study visits on days 1 (booster vaccination), 8, 15, 29, and 180. Predefined local (injection site) and systemic solicited adverse events were reported by participants completing an e-diary, which was distributed with training on day 1 and collected by investigators on day 8. Unsolicited adverse events were recorded to the end of day 29 at study visits. Participants were queried at each visit for COVID-19 diagnosis; those presenting with COVID-19 symptoms were tested by RT-PCR. Serious adverse events, medically attended adverse events, and adverse events of special interest (appendix p 5) were recorded to the end of day 180.

Serum samples for immunogenicity analyses and SARS-CoV-2 serology assessment and blood samples for assessing cell-mediated responses and for sequencing were collected on days 1 (before dosing), 15, 29, and 180. Serological responses to spike protein from ancestral SARS-CoV-2 and variants of concern were assessed quantitatively by means of a validated multiplexed electrochemiluminescence-based immunoassay (appendix p 5). SARS-CoV-2 neutralising antibody levels were measured by means of validated pseudovirus

neutralisation assays (appendix pp 6, 9). SARS-CoV-2 cellular responses were measured by means of interferon-γ enzyme-linked immunospot (ELISpot) and intracellular cytokine staining assays (appendix pp 6–7).

Outcomes

The primary safety objective was to characterise the safety and tolerability of an AZD2816 booster in baseline-seronegative participants previously vaccinated with AZD1222 by evaluating local and systemic solicited adverse events to the end of day 8 and unsolicited adverse events, including serious adverse events, medically attended adverse events, and adverse events of special interest, as well as safety laboratory measurements, to the end of day 29. Secondary, prespecified safety objectives were to similarly characterise the safety and tolerability of an AZD1222 booster in baseline-seronegative participants previously vaccinated with AZD1222, and of AZD1222 and AZD2816 booster doses following an mRNA vaccine primary series. Additional secondary safety objectives were to characterise the extended safety of each primary series–booster combination in terms of the incidence of serious adverse events, medically attended adverse events, and adverse events of special interest to the end of day 180.

Per protocol, the primary immunogenicity objective was to establish whether the humoral immune response against beta elicited by an AZD2816 booster in participants previously vaccinated with AZD1222 is non-inferior to that against ancestral SARS-CoV-2 elicited by a two-dose AZD1222 primary series in a historical control group, on the basis of the ratio of geometric mean titres (GMTs) of pseudovirus neutralising antibodies 28 days after the booster or second dose of primary-series AZD1222. The historical control group comprised participants who received AZD1222 in a phase 3 trial,[16] matched on the basis of age, sex, BMI, and baseline comorbidities (appendix p 7). The protocol-specified hierarchy of primary and key secondary immunogenicity objectives plus other secondary immunogenicity objectives is shown in the appendix (pp 11–12). Following database lock for an interim analysis, on Nov 17, 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use requested changes in the hierarchy of immunogenicity objectives in the statistical analysis plan (SAP) and also that the original primary analysis be separated into three individual SAPs specific to the AZD1222 previously vaccinated cohort; the mRNA previously vaccinated cohort; and the previously unvaccinated cohort (not reported herein). The revised immunogenicity objective hierarchies are summarised in the appendix (pp 11–12); full details of the MHRA and EMA requests are provided in the appendix (pp 7–8). The SAPs are also provided in the appendix.

Per the revised SAPs, within each of the AZD1222 and mRNA vaccine previously vaccinated cohorts, the primary objective was to establish non-inferiority of pseudovirus neutralising antibody GMT on day 29 following an AZD1222 booster versus an AZD1222 primary series in historical controls. Key secondary and other secondary objectives with the endpoint of GMT ratio are shown in the appendix (pp 11–12). Additional secondary immunogenicity objectives included comparisons based on seroresponse (≥4-times increase in pseudovirus neutralising antibodies from baseline, as evaluated via geometric mean fold-rise) rate. Exploratory immunogenicity objectives included assessment of antibody responses against selected SARS-CoV-2 variants of concern and in baseline-seropositive participants, and assessment of cellular immune responses following booster dosing in subgroups of participants. Selected variants of concern included omicron BA.1, on the basis of the timing of variant emergence during the conduct of the study.

Statistical analysis

The safety analysis population included all participants who received an AZD1222 or AZD2816 booster, analysed according to treatment received. Rates of solicited adverse events were analysed using the number of participants for whom e-diary data were available as the denominator. The immunogenicity analysis set included all randomly assigned participants who received an AZD1222 or AZD2816 booster (analysed according to treatment received), had baseline and post-dose antibody measurements, had at least one post-dose quantifiable serum titre, and had no protocol deviations that potentially could have interfered with generating or interpreting an antibody response. Analysis populations are detailed in the protocol (appendix).

1300 baseline-seronegative participants were planned for enrolment in the previously vaccinated cohorts, with approximately 700 previously vaccinated with AZD1222 vaccine and 600 previously vaccinated with an mRNA vaccine. The study was originally designed as descriptive for the primary objective, and sample sizes were justified with precision estimates based on data variation within previous studies of AZD1222 primary-series vaccination (protocol; appendix); comparisons were subsequently added, and power to detect differences was established on the basis of standard guidelines for non-inferiority margins.[20] Sample sizes were fixed at 350 participants per previous AZD1222 cohort and 300 participants per previous mRNA vaccine cohort to provide greater than 99% power to show non-inferiority in terms of GMT ratio, assuming no difference between cohorts with a non-inferiority margin of 0·67, and 77·2% power to show non-inferiority in terms of seroresponse rate with a non-inferiority margin of –10%, assuming an observed response rate of 59·7%.

Three interim analyses were planned (appendix p 8). This manuscript reports the final analysis of the booster component of the study, which was done when all previously vaccinated participants had completed or

discontinued before their day 180 post-booster visit. Statistical comparisons were done per the hierarchies in the revised SAPs (appendix pp 11–12).

For immunogenicity assessment, GMTs and geometric mean fold-rise (GMFR) values were calculated as described in the appendix (p 7). All analyses were done with the SAS statistical software suite, version 9.4 or higher. For immunogenicity non-inferiority comparisons, all

comparisons of GMT ratios were made using the lower bound of two-sided score-based CIs ($\alpha=0.05$), with a non-inferiority margin of 0.67 (lower bound)/1.5 (upper bound).[20] All non-inferiority comparisons of seroresponse rates were made using the lower bound of two-sided score-based CIs ($\alpha=0.05$) with a non-inferiority margin of –10% as specified by the EMA.[20] Within each primary-series cohort, a hierarchical approach was used to control for
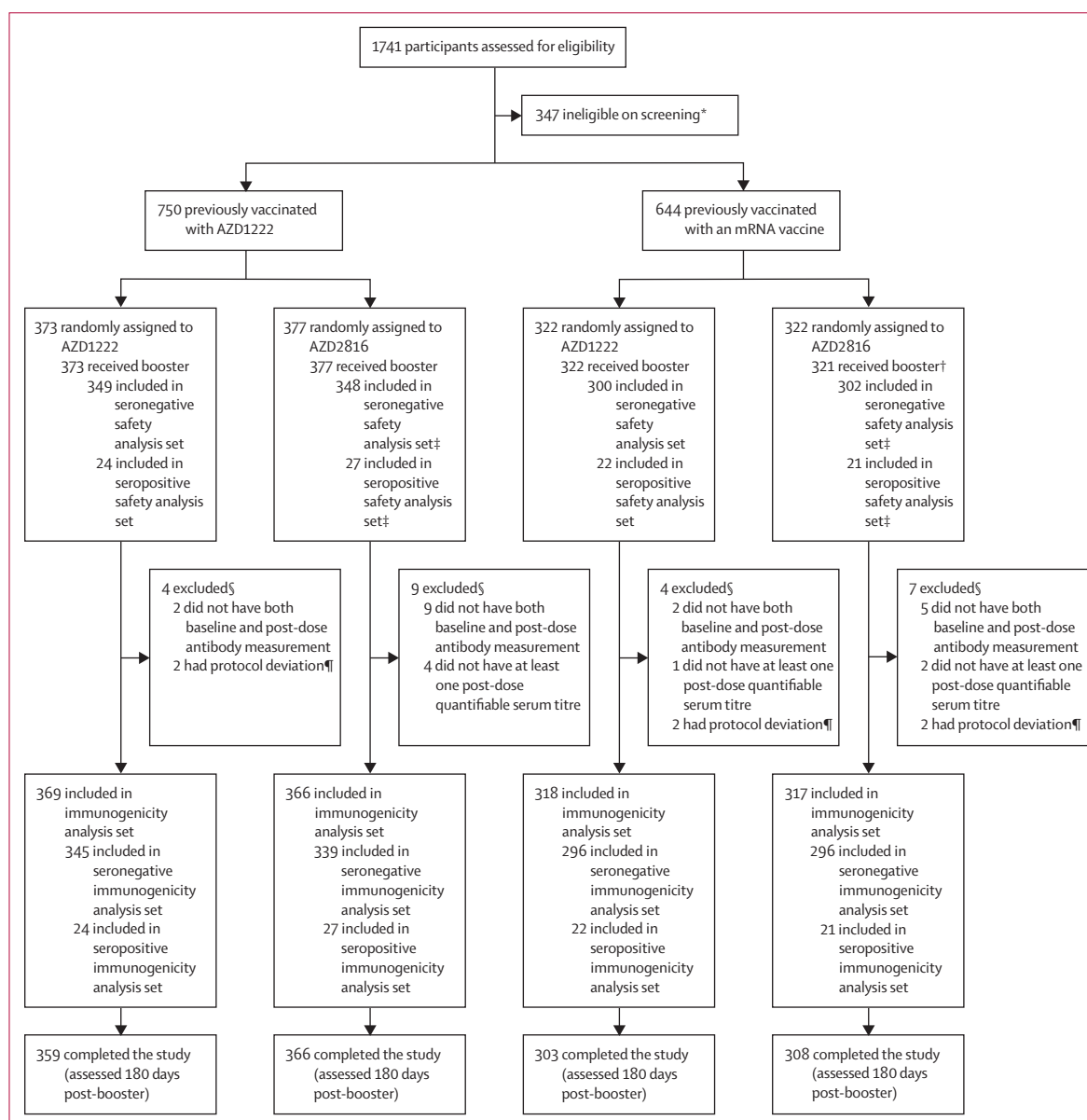

Figure 1: Trial profile

The number of participants who were screened and who were found to be ineligible on screening includes some participants who were previously unvaccinated. These participants might have been eligible to participate in the two-dose primary-series cohort of the study, but they were considered ineligible on screening for the purposes of this previously vaccinated cohort. *279 did not meet eligibility criteria; 13 withdrew; 7 were not randomly assigned on the basis of sponsor decision; 3 were lost to follow-up; 38 were not randomly assigned for other reasons; and 7 were not randomly assigned for unknown reasons. †1 withdrew consent after random assignment. ‡n=2 participants (1 seronegative, 1 seropositive) randomly assigned to receive AZD2816 booster following an AZD1222 primary series were subsequently found to have been previously vaccinated with an mRNA vaccine and were analysed in the AZD2816 booster–mRNA primary-series group. §Participants could be excluded for more than one reason. ¶Protocol deviations judged to have the potential to interfere with antibody response evaluation.

multiplicity of testing of the primary and key secondary immunogenicity endpoints in order, each with a type I error rate of 5%. Testing of each subsequent endpoint only occurred on rejection of the null hypothesis of each previous endpoint in the hierarchy (appendix pp 11–12). A data monitoring committee was used. This study is registered with ClinicalTrials.gov, NCT04973449.

Role of the funding source
The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results
Of the 1741 participants screened, 1394, of whom 750 and 644 were previously vaccinated with an AZD1222 or mRNA vaccine primary series, respectively, were randomly assigned and 1393 received an AZD1222 or AZD2816 booster between June 27 and Sept 30, 2021 (figure 1). Baseline characteristics in this safety population were similar between randomised groups within each primary-series cohort (table 1). Compared with those who had received an mRNA vaccine, participants who had received an AZD1222 primary series were older (348 [47%] of 748 vs 169 [26%] of 645, aged ≥65 years) and less likely to be female (343 [46%] of 748 vs 390 [60%] of 645), and had a longer median interval since primary-series completion (table 1). Of 1394 randomly assigned participants, 1336 (95·8%) completed the study (day 180 assessment). The seronegative immunogenicity analysis population comprised 1276 participants (figure 1; appendix p 13).

Data on solicited adverse events were available from 1281 participants in the seronegative safety population (appendix pp 14, 28). Among participants previously vaccinated with AZD1222, rates of solicited adverse events following AZD1222 and AZD2816 boosters overall were 266 (78%) of 340 and 275 (80%) of 343, respectively, of local solicited adverse events were 209 (61%) of 340 and 225 (66%) of 343 respectively, and of systemic solicited adverse events were 206 (61%) of 340 and 211 (62%) of 343, respectively. Solicited adverse events were most frequently reported on days 1–4 (appendix p 28), and most were mild or moderate; six (2%) of 340 and 14 (4%) of 343 participants reported grade 3 or higher solicited adverse events after AZD1222 and AZD2816 boosters, respectively (appendix pp 14, 28). In participants who received an mRNA vaccine primary series, rates of solicited adverse events following AZD1222 and AZD2816 boosters were 269 (90%) of 299 and 277 (93%) of 299, respectively, with rates of grade 3 or higher events of 36 (12%) of 299 and 47 (16%) of 299. One grade 4 solicited adverse event of fatigue was reported following AZD2816 (mRNA vaccine primary series); the participant had a concurrent vasovagal event without impairment or loss of consciousness on day 2, resulting in an emergency department visit. One grade 4 solicited adverse event of headache was reported on day 6 following AZD1222 (AZD1222 primary series), which led to an emergency department visit; it was considered not related to study intervention by an investigator. Across all groups, the most common local solicited adverse events were injection site pain and tenderness, and the most common systemic solicited adverse events were fatigue, headache, malaise, and muscle pain (appendix p 14). Solicited adverse events in the overall safety population are summarised in the appendix (p 15).

In the seronegative safety population, unsolicited adverse events to the end of day 29 were reported in 151 (22%) of 697 participants who received an AZD1222 vaccine primary series and 152 (25%) of 602 participants who received an mRNA vaccine primary series (table 2; appendix [p 16], for data in the overall safety population), including grade 3 events in 17 (2%) of 697 and

	AZD1222 (n=748)		mRNA vaccine (n=645)*	
	AZD1222 (n=373)	AZD2816 (n=375)	AZD1222 (n=322)	AZD2816 (n=323)
Age at randomisation, years	63 (49–71)	63 (51–72)	55 (46–65)	54 (47–66)
18–64 years	199 (53%)	201 (54%)	238 (74%)	238 (74%)
≥65 years	174 (47%)	174 (46%)	84 (26%)	85 (26%)
Sex†				
Male	201 (54%)	204 (54%)	125 (39%)	130 (40%)
Female	172 (46%)	171 (46%)	197 (61%)	193 (60%)
Race				
White	325 (87%)	326 (87%)	290 (90%)	290 (90%)
Black	2 (<1%)	1 (<1%)	3 (1%)	2 (1%)
Asian	10 (3%)	14 (4%)	8 (2%)	13 (4%)
Mixed	0	1 (<1%)	2 (1%)	0
Not reported or unknown	36 (10%)	33 (9%)	19 (6%)	18 (6%)
Country‡				
UK	354 (95%)	357 (95%)	319 (99%)	315 (98%)
Poland	19 (5%)	18 (5%)	3 (1%)	8 (2%)
Comorbidities				
Any	165 (44%)	163 (43%)	143 (44%)	145 (45%)
BMI ≥30 kg/m²	92 (25%)	91 (24%)	99 (31%)	98 (30%)
Significant cardiovascular disease	103 (28%)	100 (27%)	70 (22%)	67 (21%)
Chronic lung disease	12 (3%)	15 (4%)	15 (5%)	20 (6%)
Diabetes	26 (7%)	14 (4%)	9 (3%)	19 (6%)
None	208 (56%)	214 (57%)	179 (56%)	176 (55%)
Time since primary series, days	261 (112–308)	262 (117–304)	119 (107–141)	123 (110–141)
Primary series dosing interval, days	59 (32–73)	56 (32–70)	70 (62–76)	70 (57–76)
SARS-CoV-2 serostatus at baseline				
Negative	349 (94%)	350 (93%)	300 (93%)	300 (93%)
Positive	24 (6%)	27 (7%)	22 (7%)	21 (7%)

Data shown are n (%) or median (IQR). Participant demographics and clinical characteristics of participants receiving a third-dose booster of AZD1222 or AZD2816 following a two-dose primary series of AZD1222 or an mRNA vaccine. *All participants in the mRNA vaccine primary-series cohort in this analysis had received a primary series of BNT162b2, due to the timing of the study and the locations of participating sites. †Self-reported. ‡Accrual by centre is shown in the appendix (p 26).

Table 1: Baseline characteristics of the safety population

ten (2%) of 602. The most common unsolicited adverse events were headache (29 [2%] of 1299 overall) and fatigue (28 [2%] of 1299). Rates of unsolicited adverse events considered related to booster vaccine were 33 (5%) of 697 in participants who received an AZD1222 vaccine primary series and 50 (8%) of 602 in participants who received an mRNA vaccine primary series, with fatigue reported in 12 participants overall and all other related adverse events reported in fewer than ten participants (appendix pp 17–18).

No participants discontinued the study because of adverse events. To the end of day 180, rates of serious adverse events were no more than 2% and adverse events of special interest were no more than 12%, across all groups in the seronegative safety population (table 2). No serious adverse event was reported in more than one participant (appendix p 19). Individual medically attended adverse events (appendix pp 20–24) and adverse events of special interest (appendix p 25) were all reported in no more than 2% of participants per group, with most events reported in only one participant (<1%). One participant had an adverse event with an outcome of death due to pancreatic adenocarcinoma (considered unrelated to study intervention). COVID-19 adverse events were reported in 73 (10%) of 697 participants who received an AZD1222 vaccine primary series and 51 (8%) of 602 participants who received an mRNA vaccine primary series (table 2), none of which were serious adverse events.

AZD1222 and AZD2816 boosters following an AZD1222 primary series elicited strong humoral immune responses against ancestral SARS-CoV-2, with GMFRs of pseudovirus neutralising antibody GMT from day 1 to day 29 of 6·53 (95% CI 5·60–7·62) and 6·02 (5·21–6·94), respectively, and against the beta variant (GMFRs of 7·60 [6·41–9·01] and 14·59 [12·47–17·08], respectively; appendix p 29). Humoral immune responses in participants who received an mRNA vaccine primary series are shown in the appendix (p 29); GMFRs of pseudovirus neutralising antibody GMT from day 1 to day 29 against ancestral SARS-CoV-2 were 3·76 (95% CI 3·25–4·35) and 4·71 (4·00–5·53), respectively, and against beta were 5·90 (5·05–6·89) and 14·52 (12·17–17·34), respectively. Pseudovirus neutralising antibody responses remained elevated at day 180 compared with baseline, with some degree of waning from day 29.

The primary immunogenicity endpoint was met: GMT against ancestral SARS-CoV-2 on day 29 after an AZD1222 booster (following either primary series) was non-inferior to that on day 29 post-dose 2 of an AZD1222 primary series (historical control cohort); GMT ratios were 1·02 (95% CI 0·90–1·14) with an AZD1222 booster following an AZD1222 vaccine primary series and 3·47 (3·09–3·89) with an AZD1222 booster following an mRNA vaccine primary series (figure 2). All key secondary immunogenicity objectives were also met with an AZD2816 booster (following either primary series), with non-inferiority of neutralising antibody GMT shown

	AZD1222 (n=697)		mRNA vaccine (n=602)	
	AZD1222 (n=349)	AZD2816 (n=348)	AZD1222 (n=300)	AZD2816 (n=302)
Any unsolicited adverse event to the end of 28 days post-dose	81 (23%)	70 (20%)	73 (24%)	79 (26%)
Grade 1	34 (10%)	40 (11%)	51 (17%)	46 (15%)
Grade 2	39 (11%)	21 (6%)	18 (6%)	27 (9%)
Grade 3	8 (2%)	9 (3%)	4 (1%)	6 (2%)
Any related unsolicited adverse event	20 (6%)	13 (4%)	24 (8%)	26 (9%)
Unsolicited adverse events in ≥10 participants				
Headache	5 (1%)	4 (1%)	8 (3%)	12 (4%)
Fatigue	5 (1%)	10 (3%)	8 (3%)	5 (2%)
Myalgia	4 (1%)	4 (1%)	6 (2%)	1 (<1%)
Diarrhoea	1 (<1%)	2 (1%)	8 (3%)	3 (1%)
Oropharyngeal pain	5 (1%)	3 (1%)	4 (1%)	0
Arthralgia	2 (1%)	4 (1%)	2 (1%)	4 (1%)
Events to the end of 28 days post-dose				
Any serious adverse event	0	0	0	1 (<1%)
Adverse event leading to study discontinuation	0	0	0	0
Any medically attended adverse event	34 (10%)	26 (7%)	16 (5%)	24 (8%)
Any adverse event of special interest	3 (1%)	1 (<1%)	6 (2%)	6 (2%)
Any adverse event with outcome of death	0	0	0	0
Events to the end of 180 days post-dose				
Any serious adverse event	6 (2%)	7 (2%)	3 (1%)	4 (1%)
Any medically attended adverse event	72 (21%)	65 (19%)	47 (16%)	58 (19%)
Any adverse event of special interest	41 (12%)	42 (12%)	31 (10%)	33 (11%)
Any adverse event with outcome of death	0	1 (<1%)	0	0
Any COVID-19 adverse event	37 (11%)	36 (10%)	24 (8%)	27 (9%)
Time to confirmed COVID-19 adverse events post-dose, days	159 (124–170)	154 (96–171)	160 (115–176)	155 (92–173)

Data shown are n (%) or median (IQR).

Table 2: Summary of unsolicited adverse events reported to the end of 28 days post-dose and serious adverse events, medically attended adverse events, and adverse events of special interest reported to the end of 180 days post-dose in the seronegative safety population

for all prespecified day-29 comparisons (figure 2). Compared with an AZD1222 booster, AZD2816 elicited greater responses against beta (GMT ratios—AZD1222 primary series, 1·84 [95% CI 1·63–2·08]; mRNA vaccine primary series, 2·22 [1·99–2·47]) and non-inferior responses against ancestral SARS-CoV-2 (GMT ratios—AZD1222 primary series, 0·87 [0·78–0·97]; mRNA vaccine primary series, 1·25 [1·13–1·39]).

Seroresponse rates against ancestral SARS-CoV-2 and beta with an AZD1222 or AZD2816 booster were at least 66% following an AZD1222 primary series and at least 43% following an mRNA vaccine primary series (appendix p 30). In the AZD1222 and mRNA vaccine primary-series groups, the highest seroresponse rates—265 (83%) of 320 (95% CI 78–87) and 223 (81%) of 277 (75–85), respectively—were observed against beta with an AZD2816 booster. Comparisons of seroresponse rates are shown in the appendix (p 30).
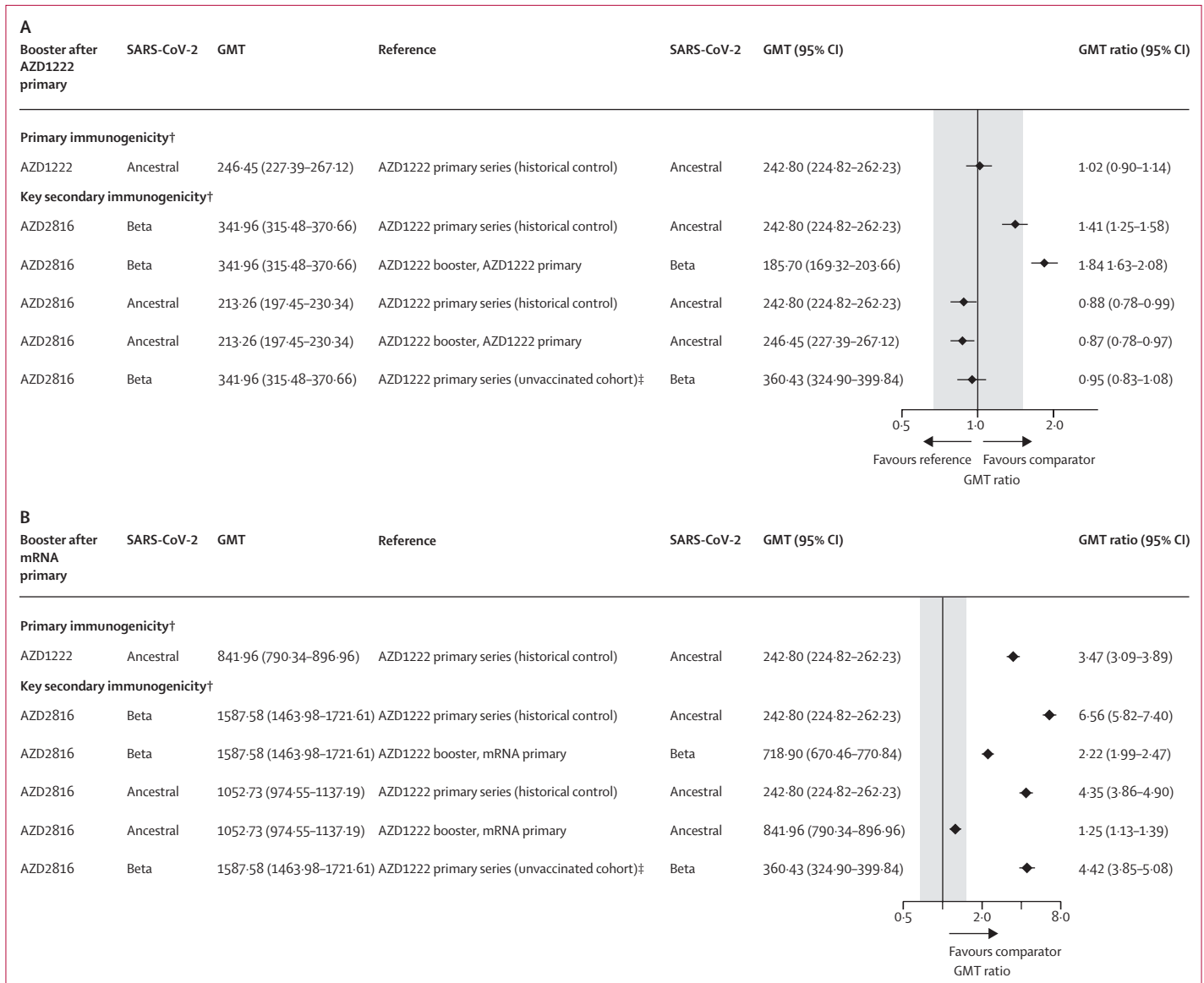
A

Booster after AZD1222 primary	SARS-CoV-2	GMT	Reference	SARS-CoV-2	GMT (95% CI)	GMT ratio (95% CI)
Primary immunogenicity†						
AZD1222	Ancestral	246·45 (227·39–267·12)	AZD1222 primary series (historical control)	Ancestral	242·80 (224·82–262·23)	1·02 (0·90–1·14)
Key secondary immunogenicity†						
AZD2816	Beta	341·96 (315·48–370·66)	AZD1222 primary series (historical control)	Ancestral	242·80 (224·82–262·23)	1·41 (1·25–1·58)
AZD2816	Beta	341·96 (315·48–370·66)	AZD1222 booster, AZD1222 primary	Beta	185·70 (169·32–203·66)	1·84 1·63–2·08)
AZD2816	Ancestral	213·26 (197·45–230·34)	AZD1222 primary series (historical control)	Ancestral	242·80 (224·82–262·23)	0·88 (0·78–0·99)
AZD2816	Ancestral	213·26 (197·45–230·34)	AZD1222 booster, AZD1222 primary	Ancestral	246·45 (227·39–267·12)	0·87 (0·78–0·97)
AZD2816	Beta	341·96 (315·48–370·66)	AZD1222 primary series (unvaccinated cohort)‡	Beta	360·43 (324·90–399·84)	0·95 (0·83–1·08)

0·5   1·0   2·0

Favours reference ← → Favours comparator
GMT ratio

B

Booster after mRNA primary	SARS-CoV-2	GMT	Reference	SARS-CoV-2	GMT (95% CI)	GMT ratio (95% CI)
Primary immunogenicity†						
AZD1222	Ancestral	841·96 (790·34–896·96)	AZD1222 primary series (historical control)	Ancestral	242·80 (224·82–262·23)	3·47 (3·09–3·89)
Key secondary immunogenicity†						
AZD2816	Beta	1587·58 (1463·98–1721·61)	AZD1222 primary series (historical control)	Ancestral	242·80 (224·82–262·23)	6·56 (5·82–7·40)
AZD2816	Beta	1587·58 (1463·98–1721·61)	AZD1222 booster, mRNA primary	Beta	718·90 (670·46–770·84)	2·22 (1·99–2·47)
AZD2816	Ancestral	1052·73 (974·55–1137·19)	AZD1222 primary series (historical control)	Ancestral	242·80 (224·82–262·23)	4·35 (3·86–4·90)
AZD2816	Ancestral	1052·73 (974·55–1137·19)	AZD1222 booster, mRNA primary	Ancestral	841·96 (790·34–896·96)	1·25 (1·13–1·39)
AZD2816	Beta	1587·58 (1463·98–1721·61)	AZD1222 primary series (unvaccinated cohort)‡	Beta	360·43 (324·90–399·84)	4·42 (3·85–5·08)

0·5   2·0   8·0

Favours comparator →
GMT ratio

Figure 2: **Non-inferiority analyses of neutralising antibody GMT ratios with AZD1222 or AZD2816 booster doses (seronegative immunogenicity analysis population)**
Model-adjusted* pseudovirus neutralising antibody GMTs and GMT ratios with an AZD1222 booster vs historical controls and an AZD2816 booster versus historical controls or versus an AZD1222 booster following an AZD1222 primary series (A) and an mRNA vaccine primary series (B). Grey areas indicate non-inferiority bounds (lower 0·67, upper 1·5). GMT=geometric mean titre. LLoQ=lower limit of quantitation. ULoQ=upper limit of quantitation. *Model-adjusted estimates for GMT are derived using ANCOVA models that include the log-transformed value of the titre as the dependent variable, and independent variables for visit (day 1, 15, 29, and 180), baseline comorbidities (≥1 or 0), sex, and age group (18–64 years or ≥65 years) as fixed effects, time since previous vaccination as a continuous (log-transformed) covariate, and participant intercept as a random effect. Titre values measured as below the LLoQ (40) were imputed before model adjustment to a value that was half of the LLoQ. Titre values measured as more than the ULoQ (787 339) were imputed before model adjustment at the ULoQ value. †Testing hierarchies are shown per the two independent statistical analysis plans for the AZD1222 and mRNA vaccine primary-series groups. ‡Data on GMT against beta following an AZD1222 primary series are derived from a previously unvaccinated cohort in the separate primary-series component of the study (data reported elsewhere).

Anti-SARS-CoV-2 spike protein antibody responses after AZD1222 or AZD2816, following an AZD1222 or mRNA vaccine primary series (appendix p 31), were consistent with pseudovirus neutralising antibody data. Neutralising antibody responses with an AZD1222 or AZD2816 booster following an AZD1222 primary series in baseline-seropositive participants are shown in the appendix (p 32). GMTs at baseline and days 29 and 180 post-booster dose were higher than in the equivalent seronegative populations (appendix p 29), with some degree of waning at day 180.

Pseudovirus neutralising antibody responses against the delta and omicron BA.1 variants in a subset of participants who received an AZD1222 booster (n=100 per primary-series group) are shown in figure 3. GMTs against delta and omicron BA.1 increased from day 1
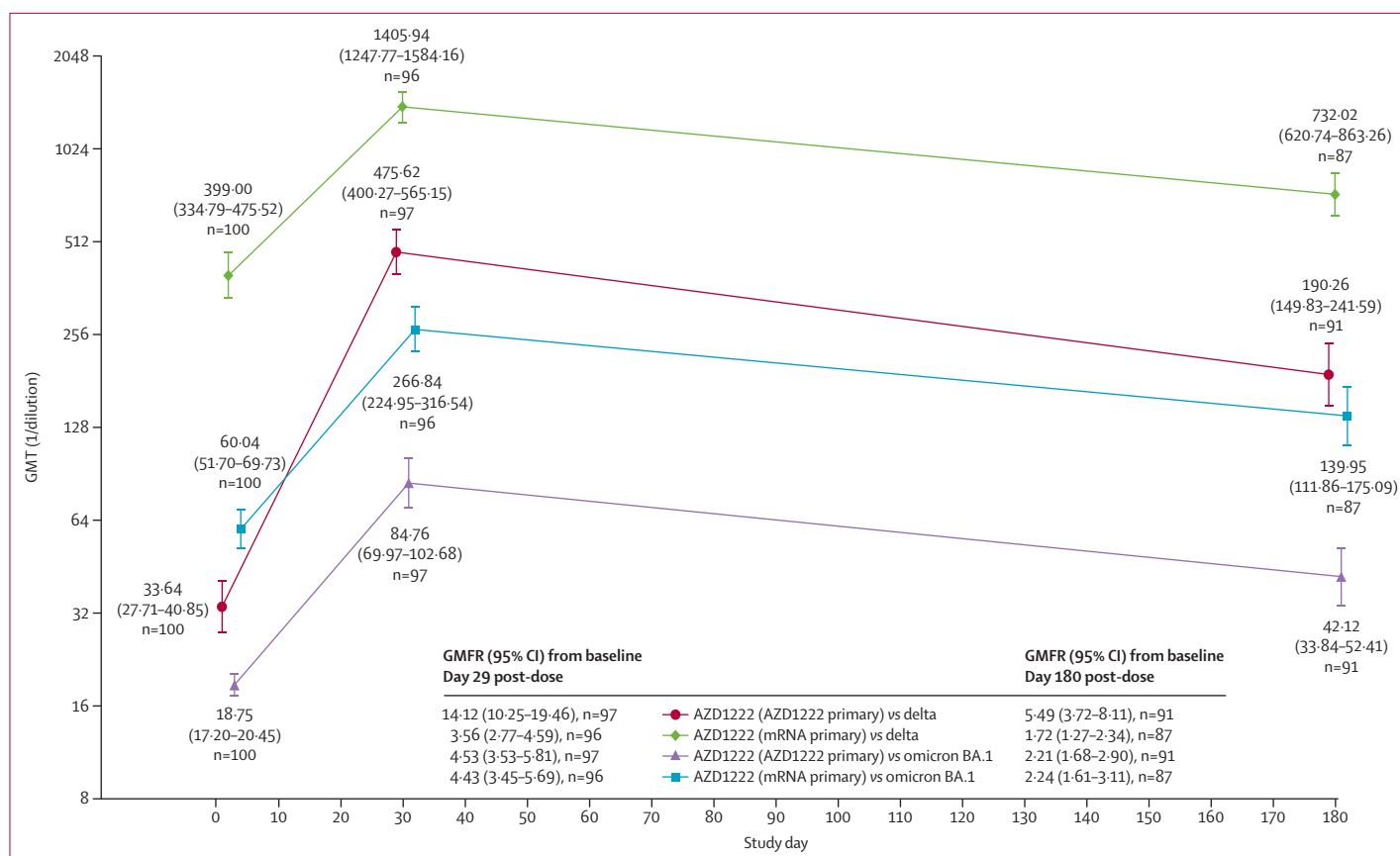
***Figure 3*: Neutralising antibody responses against the SARS-CoV-2 delta (B.1.617.2) and omicron (B.1.1.529) BA.1 variants in participants receiving an AZD1222 booster dose**
Model-adjusted* neutralising antibody titres against the SARS-CoV-2 delta and omicron BA.1 variants in a subset of participants in the seronegative immunogenicity analysis population receiving an AZD1222 booster after an AZD1222 or mRNA primary series. GMT=geometric mean titre. GMFR=geometric mean fold rise. LLoQ=lower limit of quantitation. ULoQ=upper limit of quantitation. *Model-adjusted estimates for GMT are derived by means of ANCOVA models that include the log-transformed value of the titre as the dependent variable, and independent variables for visit (day 1, 29, and 180), baseline comorbidities (≥1 or 0), sex, and age group (18–64 years or ≥65 years) as fixed effects, time since previous vaccination as a continuous (log-transformed) covariate, and participant intercept as a random effect. Titre values measured as below the LLoQ (40) were imputed before model adjustment to a value that was half of the LLoQ. Titre values measured as more than the ULoQ (787 339) were imputed before model adjustment at the ULoQ value.

to day 29, with GMFRs of 14·12 (95% CI 10·25–19·46) and 4·53 (3·53–5·81), respectively, in the AZD1222 primary-series cohort and 3·56 (2·77–4·59) and 4·43 (3·45–5·69), respectively, in the mRNA vaccine primary-series cohort, with some degree of waning from day 29 to day 180. Respective seroresponse rates on day 29 in the four groups were 75 (77%) of 97, 59 (61%) of 97, 37 (39%) of 96, and 52 (54%) of 96.

Cellular immune responses against ancestral SARS-CoV-2 were evaluated in subsets of participants (appendix p 33). Interferon-γ ELISpot assays which made use of peptide pools common to ancestral SARS-CoV-2 and beta spike proteins showed increased spike-specific T-cell responses; GMFRs were 1·69 (95% CI 1·15–2·48) and 1·82 (0·54–6·17) from day 1 to day 15 and 1·06 (95% CI 0·68–1·64) and 1·20 (0·38–3·75) to day 29 following an AZD1222 or AZD2816 booster (AZD1222 primary series), respectively. On an intracellular cytokine staining assay, spike-specific CD4+ and CD8+ T-cell responses were

observed with an AZD1222 booster following either primary series (appendix p 34) with GMFRs from day 1 of 1·000–1·549 on day 15 and 1·104–1·396 on day 29. Frequencies of polyfunctional spike-specific CD4+ T cells were increased at day 15 following either primary series and returned to below baseline by day 29 (appendix p 35). Frequencies of polyfunctional spike-specific CD8+ T cells were increased at day 15 following an AZD1222 primary series and at days 15 and 29 following an mRNA vaccine primary series (appendix p 35).

Intracellular cytokine staining was also used to assess T-cell responses on days 15 and 29 against ancestral SARS-CoV-2 and omicron BA.1 in a small number of participants receiving an AZD1222 booster following either primary series. Median CD4+ and CD8+ T-cell levels against ancestral SARS-CoV-2 were 0·061–0·170% and against omicron BA.1 were 0·046–0·194% on day 15 and 0·064–0·111% and 0·049–0·148% on day 29 (appendix p 33).

Discussion

These findings show that AZD1222 and AZD2816 have acceptable safety profiles and are well tolerated as third-dose booster vaccinations following an AZD1222 or mRNA vaccine primary series. Reactogenicity and rates of unsolicited adverse events with AZD1222 and AZD2816 were similar, regardless of primary series, and consistent with findings from previous trials of AZD1222.[5,13–16,18] The reactogenicity of AZD1222 following an mRNA vaccine primary series was consistent with that following the first dose of an AZD1222 primary series.[16]

Until mid-2022, booster strategies exclusively made use of ancestral SARS-CoV-2 vaccines to maintain protection against severe outcomes from COVID-19.[4–6,18,21] Consistent with this and in accordance with previous studies,[5,6,18] our results showed that an AZD1222 third-dose booster provoked strongly elevated humoral responses against ancestral SARS-CoV-2 and the beta, delta, and omicron BA.1 variants, regardless of primary series. Furthermore, our immunobridging study data show that a third dose of AZD1222 boosts immunogenicity against ancestral SARS-CoV-2 and beta back to levels similar to those observed after the two-dose primary series, suggesting that booster dosing might be sufficient to restimulate very high levels of protection against severe COVID-19,[2,22] based on neutralising antibody titres being established as a correlate of protection.[23–25] These immunogenicity findings provide supportive evidence for results from real-world effectiveness studies that have shown substantial protection against severe COVID-19 with AZD1222 as a homologous or heterologous third-dose booster[5,6,18,21,26] and as a fourth-dose booster.[7] Notably, some of these studies show protection against severe disease due to omicron;[5,6,18,21,26] however, a limitation of the present study is that no immunobridging analyses were done against omicron and subvariants. These findings suggest that continued use of AZD1222 remains a valuable option to prevent severe COVID-19 and, taken together with its low cost and ease of large-scale manufacturing and distribution, it is a key component of the world's COVID-19 booster armamentarium.

Nevertheless, since August, 2022, bivalent mRNA vaccines against ancestral SARS-CoV-2 and omicron have been authorised and now form the basis of booster programmes in various geographies.[9,27] Our findings with AZD2816 reflect data on the beta-adjuvanted vaccine MVB.1.351, which produced enhanced neutralising antibody responses compared with BNT162b2 against beta, delta, omicron BA.1, and ancestral SARS-CoV-2 as a third-dose booster following a BNT162b2 primary series.[8] Similarly enhanced neutralising antibody responses have also been reported with mRNA-1273.211, a bivalent vaccine against beta and ancestral SARS-CoV-2, compared with mRNA-1273 as a third-dose booster following an mRNA-1273 primary series.[10] Beta variant-updated vaccines might thus potentially confer not only enhanced beta-specific immunity but also broad immunity against multiple SARS-CoV-2 variants. Our results show that AZD2816 not only meets the prespecified criteria for regulatory guidance on variant-specific vaccines,[20] showing an increased humoral response against beta, but also is similar to AZD1222 in restoring and enhancing humoral and cellular responses against ancestral SARS-CoV-2. Although the full clinical relevance of these data is unknown, they support the feasibility of expanding the breadth of neutralising antibodies and of successfully developing a variant-adapted vaccine by use of the ChAdOx1 platform.

Both AZD1222 and AZD2816 as third-dose boosters resulted in modest, transient increases in cellular immune responses. Following an AZD1222 booster, levels of spike-specific CD4+ and CD8+ T cells were maintained at day 29 and were similar against ancestral SARS-CoV-2 and omicron BA.1, suggesting that ancestral vaccines might prime responses that are cross-reactive or that T-cell spike epitopes are conserved between variants.[28] These data are consistent with previous studies in which cellular responses to SARS-CoV-2 have been maintained across variants in response to vaccination, with up to 84% of spike-specific CD4+ and CD8+ T-cell responses on intracellular cytokine staining assays in participants vaccinated with BNT162b2 or Ad26.CoV2.S showing cross-reactivity to omicron, beta, and delta variants.[29,30] Data on cellular immune responses to bivalent vaccines will be important in this context.

A challenge with variant-adapted vaccines is the development timescale and the potential for rapid emergence of new, antigenically distinct SARS-CoV-2 variants. A limitation of this study is that since it commenced, beta has ceased to be a circulating variant of concern and multiple COVID-19 waves driven by the delta variant and omicron subvariants have occurred; the same is true for variant-adapted vaccines against omicron BA.1 and might also soon be the case for those against omicron BA.4/5. Additional limitations include the relatively small population sizes for assessment of safety, the lack of participants who had previously received a two-dose primary series of mRNA-1273, which was due to study timing and site location, and the imbalances between the AZD1222 and mRNA vaccine primary-series cohorts in terms of age, sex, and time since primary series, which were associated with differences in AZD1222 and mRNA vaccine distribution and use under vaccination policies in the UK and Poland. Finally, our study was not designed to directly assess the efficacy of AZD1222 and AZD2816.

In conclusion, we have shown the safety and immunogenicity of AZD1222 as a third-dose homologous or heterologous booster, as well as the successful development of the beta variant-adapted vaccine AZD2816 with the ChAdOx1 platform. Although bivalent mRNA vaccines form the basis for booster strategies in many countries, our findings support the continued protection conferred by ancestral SARS-CoV-2 vaccines

against severe COVID-19 due to circulating variants. Our findings also suggest that AZD1222 remains an important accessible option for booster dosing to prevent hospitalisation and death associated with COVID-19 worldwide, particularly as a practicable option for low-to-middle-income countries where logistical challenges with storage and distribution and financial challenges might preclude using certain booster vaccines.

References
1 Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022; **22:** 1293–302.
2 WHO. Interim statement on decision-making considerations for the use of variant updated COVID-19 vaccines. 2022. https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making-considerations-for-the-use-of-variant-updated-covid-19-vaccines (accessed March 24, 2023).
3 Wang Q, Guo Y, Iketani S, et al. Antibody evasion by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4 and BA.5. *Nature* 2022; **608:** 603–08.
4 Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. *N Engl J Med* 2022; **386:** 1532–46.
5 Costa Clemens SA, Weckx L, Clemens R, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. *Lancet* 2022; **399:** 521–29.
6 Jara A, Undurraga EA, Zubizarreta JR, et al. Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study. *Lancet Glob Health* 2022; **10:** e798–806.
7 Intawong K, Chariyalertsak S, Chalom K, et al. Reduction in severity and mortality in COVID-19 patients owing to heterologous third and fourth dose vaccines reduce severity and mortality in COVID-19 patients during the periods of delta and omicron predominance in Thailand. *Int J Infect Dis* 2023; **126:** 31–38.
8 Launay O, Cachanado M, Luong Nguyen LB, et al. Immunogenicity and safety of beta-adjuvanted recombinant booster vaccine. *N Engl J Med* 2022; **387:** 374–76.
9 Chalkias S, Harper C, Vrbicky K, et al. A bivalent Omicron-containing booster vaccine against COVID-19. *N Engl J Med* 2022; **387:** 1279–91.
10 Chalkias S, Eder F, Essink B, et al. Safety, immunogenicity and antibody persistence of a bivalent Beta-containing booster vaccine against COVID-19: a phase 2/3 trial. *Nat Med* 2022; **28:** 2388–97.
11 Spencer AJ, Morris S, Ulaszewska M, et al. The ChAdOx1 vectored vaccine, AZD2816, induces strong immunogenicity against SARS-CoV-2 beta (B.1.351) and other variants of concern in preclinical studies. *EBioMedicine* 2022; **77:** 103902.
12 Cele S, Gazy I, Jackson L, et al. Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. *Nature* 2021; **593:** 142–46.
13 Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; **396:** 467–78.
14 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. *Lancet* 2021; **397:** 99–111.
15 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. *Lancet* 2021; **396:** 1979–93.
16 Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. *N Engl J Med* 2021; **385:** 2348–60.

17 Sobieszczyk ME, Maaske J, Falsey AR, et al. Durability of protection and immunogenicity of AZD1222 (ChAdOx1 nCoV-19) COVID-19 vaccine over 6 months. *J Clin Invest* 2022; **132:** e160565.

18 Munro APS, Janani L, Cornelius V, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet* 2021; **398:** 2258–76.

19 van Doremalen N, Schulz JE, Adney DR, et al. ChAdOx1 nCoV-19 (AZD1222) or nCoV-19-beta (AZD2816) protect Syrian hamsters against beta, delta and omicron variants. *Nat Commun* 2022; **13:** 4610.

20 European Medicines Agency. Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2. 2021. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant_en.pdf (accessed March 21, 2023).

21 Paul P, El-Naas A, Hamad O, et al. Effectiveness of the pre-omicron COVID-19 vaccines against omicron in reducing infection, hospitalization, severity, and mortality compared to delta and other variants: a systematic review. *Hum Vaccin Immunother* 2023; **19:** 2167410.

22 UK Medicines and Healthcare products Regulatory Agency (MHRA). Access Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines. 2021. https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines. (accessed March 21, 2023).

23 Benkeser D, Fong Y, Janes HE, et al. Immune correlates analysis of a phase 3 trial of the AZD1222 (ChAdOx1 nCoV-19) vaccine. *NPJ Vaccines* 2023; **8:** 36.

24 Fong Y, Huang Y, Benkeser D, et al. Immune correlates analysis of the PREVENT-19 COVID-19 vaccine efficacy clinical trial. *Nat Commun* 2023; **14:** 331.

25 Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27:** 2032–40.

26 Kirsebom FCM, Andrews N, Sachdeva R, Stowe J, Ramsay M, Lopez Bernal J. Effectiveness of ChAdOx1-S COVID-19 booster vaccination against the omicron and delta variants in England. *Nat Commun* 2022; **13:** 7688.

27 Business Wire. Pfizer and BioNTech announce updated clinical data for omicron BA.4/BA.5-adapted bivalent booster demonstrating substantially higher immune response in adults compared to the original COVID-19 vaccine. 2022. https://www.businesswire.com/news/home/20221103006400/en/ (accessed March 21, 2023).

28 Kingstad-Bakke B, Lee W, Chandrasekar SS, et al. Vaccine-induced systemic and mucosal T cell immunity to SARS-CoV-2 viral variants. *Proc Natl Acad Sci USA* 2022; **119:** e2118312119.

29 Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* 2022; **603:** 488–92.

30 Liu J, Chandrashekar A, Sellers D, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 omicron. *Nature* 2022; **603:** 493–96.