Final Clinical Study Report Synopsis	
Drug Substance	AZD2816/AZD1222
Study Code	D7220C00001
Edition Number	1
Date	18 January 2023
EudraCT Number	2021-002530-17
NCT Number	NCT04973449

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Final Clinical Study Report Synopsis for Previously Vaccinated Participants Receiving a Booster Vaccination of AZD1222 or AZD2816

Study dates:	First subject enrolled: 27 June 2021 Last subject last visit: 02 August 2022 The analyses presented in this report are based on a clinical database lock date of 29 September 2022
Phase of development:	Therapeutic confirmatory (II/III)
International Co-ordinating Investigator:	PPD
Sponsor's Responsible Medical Officer:	PPD

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

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Study centres

The study was conducted at 35 sites in Brazil, Poland, South Africa, and the United Kingdom (UK). There were 19 study sites in the UK and 4 study sites in Poland that randomised previously vaccinated participants.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

This Final Clinical Study Report (CSR) presents final analysis results for the previously vaccinated cohort who received a booster dose of AZD1222 or AZD2816 following primary series vaccination with AZD1222 or a messenger ribonucleic acid (mRNA) vaccine. Results for the previously unvaccinated cohort, who received a 2-dose primary series of AZD1222 and/or AZD2816, are reported separately.

The primary safety objective for the previously vaccinated cohort was to characterise the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222, based on the incidence of local and systemic solicited adverse events (AEs) for 7 days post dose, the incidence of unsolicited AEs, including medically attended AEs, serious AEs (SAEs), and AEs of special interest (AESIs), for 28 days post-dose, and the change from baseline for safety laboratory measures for 28 days post-dose. Secondary safety objectives include characterising the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222, the safety and tolerability of 1 booster dose of AZD1222 or AZD2816 in seronegative participants previously vaccinated with a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) mRNA vaccine, and the extended safety of 1 booster dose of AZD1222 or AZD2816 through 6 months post-vaccination.

The primary and key secondary immunogenicity objectives for the previously vaccinated cohort, as specified in the study protocol, were as follows:

Primary:

1: To determine if the humoral immune response against the B.1.351 (ie, Beta) variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

Key secondary:

2.1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

2.2: To determine if the humoral immune response elicited against the B.1.351 variant by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

2.3: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

2.4: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination.

2.5: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

Following the interim analysis database lock the European Committee for Medicinal Products for Human Use (CHMP) requested that the testing hierarchy for the immunogenicity endpoints be reordered, with key secondary endpoint 2.4 becoming the primary endpoint. This final CSR presents comparative analyses of immunogenicity results according to the hierarchy requested by the CHMP. Further, what was key secondary 2.1 was demoted to key secondary 2.5 on the basis that critical differences between the previously vaccinated and previously unvaccinated cohorts were likely to confound the interpretation of the results.

Study design

This was a Phase II/III partially double-blinded, randomised, multinational, active-controlled study to evaluate the safety and immunogenicity of AZD2816 as a 1-dose booster vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants. This study also investigated the safety and immunogenicity of 1) a 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a 1-dose booster of AZD1222 in participants previously vaccinated with a 2-dose coronavirus disease 2019 (COVID-19) vaccine. This report presents final results for the cohort of participants who were previously vaccinated with a 2-dose COVID-19 vaccine and received either AZD2816 or AZD1222 in this study as a booster vaccination.

Target population and sample size

The study cohorts were selected to represent real-world conditions, including heterologous dosing. The target population for the previously vaccinated cohort was approximately 700 seronegative adults who had received 2 doses of AZD1222 and 600 seronegative adults who had received 2 doses of an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). These participants were to be randomised 1:1 to 1 dose of either AZD1222 or AZD2816. In addition, seropositive participants, capped at 10% of the seronegative population, were to be randomised 1:1 to 1 dose of either AZD1222 or AZD2816.

The booster dose of AZD1222 or AZD2816 was to be administered at least 90 days after the second dose of AZD1222 or mRNA vaccine.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Study intervention was 1 booster dose of either AZD1222 or AZD2816 at nominal doses of 5×10^{10} viral particles ($\geq 2.5 \times 10^{8}$ infectious units). CCI [redacted]
CCI [redacted]

Duration of treatment

Study intervention was a single booster vaccine dose.

Statistical methods

The overall hypothesis for this study was that 28 days after vaccination (ie, following a single booster dose for the previously vaccinated participants or a second vaccination dose for previously unvaccinated participants), AZD2816 would be non-inferior to AZD1222 in terms of immunogenicity (ie, neutralising antibodies [nAb] geometric mean titre [GMT] ratio and difference in seroresponse rates).

The hypothesis specific to the treatment groups receiving a booster dose of AZD1222 was that 28 days after a single booster dose, boosting with AZD1222 would be non-inferior to a primary 2-dose vaccination series with AZD1222 in terms of immunogenicity.

All non-inferiority comparisons of GMT ratios were made utilising the lower bound of two-sided score-based confidence intervals (CIs) ($\alpha = 0.05$) with non-inferiority margin 0.67. All non-inferiority comparisons of seroresponse rates were made utilising the lower bound of two-sided score-based CIs ($\alpha = 0.05$) with non-inferiority margin -10%.

Study population

Of the 1394 previously vaccinated participants randomised and included in the final analysis dataset, Day 29 data are available for 99.0% and 95.8% completed the study. The disposition of participants was generally balanced across treatment groups. In the seronegative analysis sets, there were few important protocol deviations that could interfere with the immunogenicity or safety analyses. The use of prohibited concomitant medications, with the exception of additional COVID-19 vaccinations (ie, 4th dose boosters) late in the 6-month follow-up period, was rare. Demographic and baseline characteristics were generally balanced between the AZD1222 and AZD2816 treatment groups within each cohort. Furthermore, the historical control cohort of participants in study D8110C00001 treated with 2 doses of AZD1222 was well-matched with the AZD1222 cohort in this study. These parameters allowed for a robust assessment of the safety, tolerability, and immunogenicity of AZD1222 and AZD2816 booster doses.

While the demographic and baseline characteristics of study participants were generally balanced between the AZD1222 and AZD2816 treatment groups within each cohort, there were some differences between the AZD1222 and mRNA cohorts for the Seronegative Immunogenicity Analysis Set. In the mRNA cohort, participants were younger (median 55 years compared with 62 years in the AZD1222 cohort), and more were female (approximately 60% compared with 46% in the AZD1222 cohort). Furthermore, the time since primary series vaccination was shorter for the mRNA cohort (median approximately 4 months) compared with the AZD1222 cohort (median approximately 9 months). These differences were due, in part, to the differential vaccine rollout strategy in the UK for AZD1222 and mRNA vaccines. To mitigate the impact of these differences, model-adjusted immunogenicity analyses, and subgroup analyses of the immunogenicity and safety data, were conducted.

Summary of immunogenicity results

Non-inferiority of booster doses of AZD1222 and AZD2816 was demonstrated for the primary and all key secondary endpoints. Specifically, the humoral immune response to a booster dose of AZD1222 is non-inferior to the response elicited by primary vaccination with AZD1222 (AZD1222 cohort GMT ratio: 1.02 [95% CI 0.90, 1.14]; mRNA cohort GMT ratio: 3.47 [95% CI 3.09, 3.89]). Strong humoral responses to SARS-CoV-2 were observed by 28 days after booster doses of either AZD1222 or AZD2816 in seronegative participants previously vaccinated with AZD1222 or an mRNA vaccine:

- Against the Wuhan-Hu-1 strain, similar fold rises in GMT levels were observed after booster doses of AZD1222 or AZD2816 within both the AZD1222 (fold rise: 6.02 to 6.53) and mRNA (fold rise: 3.76 to 4.71) cohorts.
- Against the Beta variant, increased GMT levels against the Beta variant were observed after booster doses of AZD1222 or AZD2816, though the response in pseudoneutralising antibodies was greater after a booster of AZD2816 (fold rise: 14.52 to 14.59) than after a

booster of AZD1222 (fold rise: 5.90 to 7.60). This difference was observed in both the mRNA and AZD1222 cohorts.

- Many participants in all treatment groups had a seroresponse (≥ 4-fold increase in titre from baseline in pseudoneutralising antibodies) following booster doses of AZD1222 or AZD2816.
- The responses to booster doses of AZD1222 and AZD2816 were generally similar when assessed by subgroups of sex and comorbidity status. Small numerical decreases in immunogenicity were observed in participants ≥ 65 years of age (compared with < 65-year-olds), which has previously been shown not to decrease clinical efficacy.
- The responses following booster doses of AZD1222 and AZD2816 to the Delta variant were generally consistent with those observed for the Wuhan-Hu-1 strain and Beta variant. While baseline GMTs were lower against the Omicron BA.1 variant compared with the Wuhan-Hu-1 strain, a booster dose of AZD1222 was still associated with a > 4-fold rise in titres in both the AZD1222 and mRNA cohorts.
- At 6 months post-booster doses of AZD1222 and AZD2816 there was durability of immune response. Neutralising and binding antibody responses waned from the peaks observed by Day 29 but remained notably higher than baseline values in both the AZD1222 and mRNA cohorts, including against the Delta and Omicron BA.1 variants.
- Cellular immune responses to Spike (Wuhan + common S1/S2 peptides) were increased above baseline values at Day 15 post-booster (fold rise: 1.24 to 1.82).
- Increases in anti-vector responses, observed in all treatment groups but with minimal correlation between chimpanzee adenovirus Ox1 (ChAdOx1) pseudoneutralising antibody titres and pseudoneutralising antibody responses to SARS-CoV-2, did not perturb neutralising antibody responses to the Wuhan-Hu-1 or Beta strains.
- Humoral immune responses were also increased after a booster dose of AZD1222 or AZD2816 in seropositive participants, with peak immunogenicity GMTs above those of seronegative participants at the same timepoint.

Summary of safety results

The safety (through Day 29), extended safety (through 6 months), and reactogenicity (through Day 8) of booster doses of AZD1222 or AZD2816 in participants previously vaccinated with either AZD1222 or an mRNA vaccine, including for those in the Seronegative Safety Analysis Set, was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and AZD2816.

- Most solicited AEs were mild or moderate in intensity and of short duration. The incidence of solicited AEs was lower in males and in older adults ≥ 65 years of age, and with lower severity, than in females and in younger adults 18 to 64 years of age.
- Participants in the mRNA cohort were more likely to report a solicited AE after a booster dose of AZD1222 or AZD2816 than participants in the AZD1222 cohort. The most

common solicited AEs were tenderness and pain at the site of injection, and fatigue, headache, and muscle pain. Few participants considered their solicited AEs to be severe, but a greater proportion of solicited AEs were reported as moderate or severe in the mRNA cohort than in the AZD1222 cohort.

- Unsolicited AEs were reported in similar proportions of participants across treatment groups and across cohorts. The most frequently reported unsolicited AEs across all treatment groups were headache, fatigue, and diarrhoea. The majority of unsolicited AEs were mild to moderate in severity. No clinically meaningful differences were observed in unsolicited AEs when assessed by subgroups of age, sex, and baseline comorbidity.
- There were no deaths through Day 29. There was one death after Day 29 due to PPD (AZD1222 cohort boosted with AZD2816), reported as not related to study intervention.
- There were few SAEs, only one of which occurred before Day 29 (Appendicitis). None of the SAEs were assessed as related to study intervention.
- There were few AESIs and no clinically meaningful imbalances in the incidence of AESIs by category or preferred term at either Day 29 or at 6 months.

Conclusions

- The safety and reactogenicity of booster doses of AZD1222 or AZD2816 in participants previously vaccinated with either AZD1222 or an mRNA vaccine was generally consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified.
- Humoral immunogenicity data indicate that a booster dose of either AZD1222 or AZD2816 generates a robust humoral response to SARS-CoV-2 by 28 days after the booster is administered. Specifically, the humoral immune response to a booster dose of AZD1222 is non-inferior to the response elicited by primary vaccination with AZD1222. The immune response to a booster dose of AZD1222 or AZD2816 was consistent across all variants tested. At 6 months, neutralising and binding antibody responses waned from the peaks observed by Day 29 but remained notably higher than baseline values in both the AZD1222 and mRNA cohorts. As expected, AZD2816 generated a stronger immune response against the Beta variant than AZD1222.
- An underlying rationale for conducting this study was to assess whether a modified version of AZD1222, targeting a specific SARS-CoV-2 variant, would increase immunogenicity against that variant while maintaining immunogenicity against the original Wuhan-Hu-1 strain and other variants of concern, without any adverse impact on the safety profile. The results of the final analysis demonstrate proof-of-concept and establish that, similar to influenza vaccines, AZD1222 can be modified in the future to address emerging variants of concern.

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Drug Substance	AZD2816/AZD1222
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Edition Number	1
Date	18 January 2023
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NCT Number	NCT04973449

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Abbreviated Clinical Study Report Synopsis for Previously Unvaccinated Participants Receiving Primary Series Vaccination with AZD1222 and/or AZD2816

Study dates:	First subject enrolled: 27 June 2021 Last subject last visit: 02 August 2022 The analyses presented in this report are based on a clinical database lock date of 29 September 2022
Phase of development:	Therapeutic confirmatory (II/III)
International Co-ordinating Investigator:	PPD
Sponsor's Responsible Medical Officer:	PPD

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2 SYNOPSIS

Study centres

The study was conducted at 35 sites in Brazil, Poland, South Africa, and the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

This Clinical Study Report (CSR) presents final analysis results for the previously unvaccinated cohort who received 2 doses of AZD1222 and/or AZD2816 as primary series vaccination against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. Results for the previously vaccinated cohort, who received a single booster dose of AZD1222 and/or AZD2816 following primary series vaccination with AZD1222 or a messenger ribonucleic acid (mRNA) vaccine, are reported separately.

The primary safety objective for the previously unvaccinated cohort was to characterise the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in seronegative participants, based on:

- the incidence of local and systemic solicited adverse events (AEs) for 7 days post dose
- the incidence of unsolicited AEs, including medically attended AEs, serious AEs (SAEs), and AEs of special interest (AESIs), for 28 days post-dose, and
- the change from baseline for safety laboratory measures for 28 days post-dose.

Secondary safety objectives include characterising the safety and tolerability of primary series vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval, and 2 doses of AZD2816 with a 12-week dosing interval, in previously unvaccinated seronegative participants. Extended safety through 6 months post-vaccination was a secondary safety objective for each of these primary series combinations.

The primary and key secondary immunogenicity objectives for the previously unvaccinated cohort, according to the endpoint hierarchy requested by the CHMP and detailed in the Statistical Analysis Plan, were as follows:

Primary:

1a: To determine if the neutralizing antibody geometric mean titre (GMT) response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination with a 4-week dosing interval is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination with a 4-week dosing interval.

1b: To determine if seroresponse against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination with a 4-week dosing interval is non-inferior to seroresponse against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination with a 4-week dosing interval.

Key secondary:

2.1: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination with a 4-week dosing interval is non-inferior to the response elicited by a 2-dose AZD1222 vaccination with a 4-week dosing interval.

2.2: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose heterologous AZD1222 + AZD2816 vaccination with a 4-week dosing interval is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination with a 4-week dosing interval.

2.3: To determine if the neutralizing antibody GMT response against the original Wuhan-Hu 1 elicited by a 2-dose AZD2816 vaccination with a 4-week dosing interval is non-inferior to the response elicited by a 2 dose AZD1222 vaccination with a 4-week dosing interval.

Study design

This was a Phase II/III partially double-blinded, randomised, multinational, active-controlled study to evaluate the safety and immunogenicity of AZD2816 as a 1-dose booster vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination (4-week dosing interval) in previously unvaccinated adult participants. This study also investigated 2-dose primary series vaccination with AZD2816 with a 12-week dosing interval and with AZD1222 as first dose and AZD2816 as the second dose (4-week dosing interval). This report presents final results for the cohort of previously unvaccinated participants.

Target population and sample size

The target population for the previously unvaccinated cohort was 1290 seronegative participants. If there is no difference between treatment arm of interest (ie, a ratio of 1) the power conferred by 150 to 380 participants for the comparison of GMT ratio using a non-inferiority margin of 1.5/0.67 was > 90%.

Participants were randomised to 4 treatment groups to allow for a multitude of comparisons matching real-world pandemic conditions, including heterologous dosing and extended durations between the first and second doses. In addition, seropositive participants, capped at 10% of the seronegative population, were randomised to support exploratory analyses in these participants.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Study intervention was AZD1222 and AZD2816 at nominal doses of 5×10^{10} viral particles (≥ 2.5×10^{8} infectious units). CCI [redacted] CCI [redacted]

Duration of treatment

Study intervention was 2 doses of AZD1222, 2 doses of AZD2816, 1 dose of AZD1222 followed by 1 dose of AZD2816, all at 4-week dose intervals, or 2 doses of AZD2816 at a 12-week interval.

Statistical methods

The overall hypothesis for this study was that 28 days after vaccination (ie, following a single booster dose for the previously vaccinated participants or a second vaccination dose for previously unvaccinated participants), AZD2816 would be non-inferior to AZD1222 in terms of immunogenicity (ie, neutralising antibodies GMT ratio and difference in seroresponse rates). For the previously unvaccinated cohort, the hypothesis was that 28 days after the second dose with a 4-week dosing interval, AZD2816 would be non-inferior to AZD1222 in terms of immunogenicity. This was to be concluded only if both the co-primary endpoints (GMT ratio and difference in seroresponse) were met.

All non-inferiority comparisons of GMT ratios were made utilising the lower bound of two-sided score-based CIs ($\alpha = 0.05$) with non-inferiority margin 0.67. All non-inferiority comparisons of seroresponse rates were made utilising the lower bound of two-sided score-based CIs ($\alpha = 0.05$) with non-inferiority margin -10%.

Study population

Of the 1449 previously unvaccinated participants who were randomised, 1441 received at least one dose of AZD2816 or AZD1222. Data from 29 days post-second dose are available for 1389 (95.9%) participants and 1362 (94.0%) completed the study. The disposition of participants was generally balanced across treatment groups. In the seronegative analysis sets, there were few important protocol deviations that could interfere with the immunogenicity or safety analyses. The use of prohibited concomitant medications, with the exception of booster doses of COVID-19 vaccines received late in the study, was rare. Demographic and baseline characteristics were generally balanced between the AZD1222 and AZD2816 treatment groups within each cohort. These parameters allowed for a robust assessment of the safety, tolerability, and immunogenicity of AZD1222 and/or AZD2816 as primary series vaccination.

Summary of immunogenicity results

The non-inferiority of AZD2816 was demonstrated for the co-primary and first key secondary endpoints. The GMT ratio for the comparison of the AZD2816 treatment group (4-week

interval) against the Beta variant versus the AZD1222 treatment group against the Wuhan-Hu-1 strain was 1.19 (95% CI 1.08, 1.32) and the seroresponse difference was 1.7 (95% CI -3.1, 6.5). The GMT ratio for the comparison of the AZD2816 treatment group (4-week interval) against the Beta variant versus the AZD1222 treatment group against the Beta variant was 3.21 (95% CI 3.06, 3.36).

Summary of safety results

The safety (through 29 days post-dose), extended safety (through 6 months), and reactogenicity (through Day 8 post-dose) of AZD1222 and/or AZD2816 in previously unvaccinated participants was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles across the treatment groups.

- Most solicited AEs were mild or moderate in intensity and of short duration. The incidence of solicited AEs was lower in males and in older adults ≥ 65 years of age, and with lower severity, than in females and in younger adults 18 to 64 years of age.
- The most common solicited AEs were tenderness and pain at the site of injection, and headache and myalgia. Few participants considered their solicited AEs to be severe.
- Unsolicited AEs were reported in similar proportions of participants across treatment groups. The most frequently reported unsolicited AEs across all treatment groups were headache, upper respiratory tract infection, and COVID-19. The majority of unsolicited AEs were mild to moderate in severity. No clinically meaningful differences were observed in unsolicited AEs when assessed by subgroups of age, sex, and baseline comorbidity.
- There was one death due to PPD assessed as unrelated to study intervention by the investigator.
- There were few SAEs, with no notable imbalances between treatment groups, no PT reported in more than one participant, and none assessed as related to study intervention.
- There were few AESIs (other than VAERD) and no clinically meaningful imbalances in the incidence of AESIs by category or PT at either 29 days post-dose or at 6 months.

Conclusions

- The safety and reactogenicity of primary series vaccination with AZD1222 and/or AZD2816 in this study was generally consistent with the known safety profile of AZD1222. No emergent safety issues were identified.
- Humoral immunogenicity data demonstrate that the immune response to AZD2816 against the Beta variant is non-inferior to that of AZD1222 as against either the Wuhan-Hu-1 strain or Beta variant.
- An underlying rationale for conducting this study was to assess whether a modified version of AZD1222, targeting a specific SARS-CoV-2 variant, would increase immunogenicity against that variant while maintaining immunogenicity against the

original Wuhan-Hu-1 strain and other variants of concern, without any adverse impact on the safety profile. The results demonstrate proof-of-concept and establish that, similar to influenza vaccines, AZD1222 can be modified in the future to address emerging variants of concern.