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Efficacy, safety, pharmacokinetics, immunogenicity, and serum neutralizing activity of AZD7442 (tixagevimab-cilgavimab) in hospitalized COVID-19 patients: long-term results from the DisCoVeRy trial

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Original article:

Efficacy, safety, pharmacokinetics, immunogenicity, and serum neutralizing activity of AZD7442 (tixagevimab-cilgavimab) in hospitalized COVID-19 patients: long-term results from the DisCoVeRy trial

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Abstract

Objectives. To report long-term clinical efficacy, safety, pharmacokinetics, immunogenicity and seroneutralization results of AZD7442 (monoclonal antibodies tixagevimab-cilgavimab) in hospitalized COVID-19 patients.

Methods. In this phase 3, double-blind, randomized, multicenter trial, hospitalized adults with PCR-confirmed SARS-CoV-2 infection were randomized 1:1 to receive AZD7442 or placebo, and followed-up until day 456, with repeated blood sample collections until day 365. Clinical endpoints included clinical status, mortality, rehospitalization, SARS-CoV-2 reinfection, and adverse events. Antidrug antibodies (ADA) and serum drug concentrations were measured. Analyses were performed on the modified intention-to-treat populations, defined as participants who actually received the intervention.

Results. Between April 28, 2021, and June 23, 2022, 237 participants were randomized to AZD7442 (n=127) or placebo (n=110), and 123 participants actually received AZD7442. Participants were infected with pre-Omicron variants in 58.8% (133/226) of cases, versus 33.2% (75/226) of Omicron BA1, BA2, or BA5, and 8% (18/226) missing data. There was no significant difference in the distribution of the 7-point ordinal scale between the AZD7442 and

placebo groups, either on day 15 (primary endpoint), OR=0.93 [0.54-1.61], P=0.81, or any other time point. Significantly more rehospitalizations occurred between discharge and day 456 among participants who received AZD7442 in the global mITT population (OR=2.04 [1.03-4.05], P=0.04), but not in the antigen-positive mITT population (OR=1.78 [0.80-3.94], P=0.15). No significant differences were observed in mortality, SARS-CoV-2 reinfection, or adverse events. In the AZD7442 group, 12/87 participants (13.8%) had treatment-emergent ADA versus 5/69 (7.2%) in the placebo group (OR=2.02 [0.66-6.14], P=0.21). Serum drug concentrations were detectable up to day 365 for all sampled participants (35/35). Neutralizing antibody titres were significantly higher in the AZD7442 group up to day 180.

Conclusions. AZD7442 did not demonstrate any clinical benefit and was safe up to 15 months. This study also provides valuable data on the pharmacokinetics, immunogenicity, and neutralizing activity of AZD7442 in hospitalized COVID-19 patients.

Introduction

AZD7442 is a cocktail of two monoclonal antibodies (mAbs), tixagevimab and cilgavimab, derived from B cells obtained from patients who had recovered from SARS-CoV2 infection.[1] The fragment crystallizable (Fc) regions of the two mAbs were engineered to extend serum half-life through the YTE modification (amino acid substitutions M252Y/S254T/T256E), and to improve safety by reducing the risk of antibody-dependent enhancement of disease through the TM modification (amino acid substitutions L234F/L235E/P331S).[1]

In the context of an innovative therapeutic agent to prevent or treat infectious diseases, with a theoretically extended half-life, data on long-term patient follow-up (up to 15 months post-administration of the drug) concerning efficacy, safety and pharmacokinetics of AZD7442 are essential. Such data have already been provided for healthy individuals, and adult patients at risk of progressing to severe COVID-19 disease, either uninfected or with confirmed mild-to-moderate COVID-19.[1–4] These studies confirmed that AZD7442 was well tolerated and had a favorable safety profile up to 15 months in all patient groups.[5,6] Furthermore, serum concentration-time profiles were consistently similar for the two mAbs, were not found to be influenced by the presence of treatment-emergent antidrug antibodies (ADA), and the measured half-life of AZD7442 was approximately 90 days in all patient groups, confirming the extended half-life of both mAbs. However, no such data have yet been provided for patients hospitalized with COVID-19 and treated with 600 mg of intravenous AZD7442.

The primary analyses of the DisCoVeRy trial were conducted once all participants had completed follow-up through day 90 and were published previously,[7,8] showing no benefit or harm of AZD7442 on any clinical, virological, or safety endpoints. We report here the long-term clinical efficacy, safety, pharmacokinetics, and immunogenicity results.

Materials and methods

Study design

DisCoVeRy is a phase 3, adaptive, multicenter, randomized, double-blind, superiority trial designed to evaluate the efficacy and safety of drugs for the treatment of adults hospitalized for COVID-19 (ClinicalTrials.gov NCT04315948). The first four interventions evaluated (lopinavir/ritonavir, lopinavir/ritonavir plus IFN-b-1a, hydroxychloroquine, and remdesivir) were discontinued for futility and the results reported elsewhere.[9–11] A protocol amendment (version 14) was approved on April 20th, 2021 to evaluate AZD7442, developed by AstraZeneca. The study was conducted across 63 sites in 13 European countries (Austria, Belgium, Czech Republic, France, Greece, Hungary, Ireland, Luxembourg, Norway, Poland, Portugal, Slovakia, and Spain). The trial was approved by the Ethics Committees in each country and was sponsored by the Institut national de la santé et de la recherche médicale (Inserm, France); it was conducted in accordance with the Declaration of Helsinki.

Participants

Eligible participants were adults (≥18 years) hospitalized with SARS-CoV-2 infection confirmed on a RT-PCR performed on a nasopharyngeal (NP) swab within the 5 days preceding randomization, and a time between onset of symptoms and randomization of less than 9 days (extended to 11 days from September 20th, 2021, protocol V15). Participants with prior receipt of investigational or licensed mAb or vaccine indicated for the prevention of SARS-CoV-2 infection or COVID-19 were excluded. From September 20th, 2021, inclusion of patients with initiated (one dose) or completed (two doses) vaccination was allowed in a proportion of 20% of enrolled participants, provided they would not receive an additional dose in the 30 days following hospital discharge. Full inclusion and exclusion criteria are detailed in the appendix.

Written informed consent was obtained from all participants or their legal representative prior to randomization.

Randomization and masking

Participants were randomly assigned in a 1:1 ratio to receive AZD7442 or placebo in addition to standard of care (SoC). The randomization was stratified by region, by antigenic status obtained from the result of a rapid antigen test on a NP swab at enrolment, and, with protocol V15, by vaccination status. Randomization was performed via an electronic Case Report Form and used computer-generated blocks of various sizes. Allocation was concealed from participants, care providers, outcome assessors, and data analysts.

Procedures and assessments

The participants received a single intravenous infusion of tixagevimab-cilgavimab (600 mg at a maximum infusion rate of 50 mg/minute) or matching placebo (a 0.9% saline solution, prepared by an unblinded pharmacist) within 24 hours following randomization. Participants could not be treated with other monoclonal or polyclonal antibodies directly targeting SARS-CoV-2 during the study. The standard of care could include corticosteroids, remdesivir, and other immunomodulatory agents, at the discretion of the physician.

Participants were assessed daily while hospitalized. Follow-up assessments were scheduled on days 29 and 90 as outpatient consultations for discharged participants; on days 180 and 365 as outpatient consultations for as many patients as possible provided the center had sufficient ressources, otherwise by phone; and on day 456 by phone for all participants.

Blood samples were collected at baseline, on days 3, 8, and 15 (only for hospitalized participants), and on days 29, 90, 180 and 365 (for participants with outpatient consultations).

Endpoints

We report here: the clinical status, measured on the 7-point ordinal scale of the WHO Master Protocol v3.0, on days 15 (primary endpoint), 180 and 365; the in-hospital mortality; the mortality on days 180, 365, and 456; the occurrence of a new hospitalization between discharge from the index hospitalization and days 180, 365, and 456; and occurrence of SARS-CoV-2 reinfection between discharge from the index hospitalization and days 180, 365, and 456. Safety endpoints were recorded until day 456 and included: adverse events (AEs grade 1 through 4), serious adverse events (SAEs), disease-related adverse events (DRE). The definitions of immunogenicity endpoints follow those used in previous publications.[5,6] Treatment-emergent anti-drug antibody (TE-ADA) positivity was defined as treatment-induced (negative at baseline and at least one positive result post-baseline) or treatment-boosted (baseline titre that increased by ≥ 4 times) positivity. ADA negativity was defined as being ADA negative at all times. AZD7442 serum concentration was defined as the sum of tixagevimab and cilgavimab concentrations. Neutralizing antibody titres were measured against the Delta variant and each participants' variant of infection, and were reported as the 50% inhibitory dilution (ID50). Details are in appendix.

Populations

Clinical efficacy analyses were performed on the modified intention-to-treat (mITT) population, defined as participants for whom the infusion of the allocated treatment was actually initiated, and analyzed in their assigned randomization group. The safety population included all randomized participants, analyzed in their actual treatment group. Each population set was further categorized based on the antigenic status, defining « antigen-positive » and « global » (i.e. antigen-positive and antigen-negative) mITT and safety populations.

Statistical analyses

The clinical status measured on the 7-point ordinal scale was analyzed using a proportional odds model. The study was powered to detect an odds ratio (OR) of 1.5 (an OR greater than 1 indicates superiority of the experimental treatment over the control for each ordinal scale category), with 90% power and a two-sided type I error of 0.05, for the primary endpoint. Accounting for 5% of non-evaluable patients, 620 patients per arm were required. No interim analyses for efficacy or futility were planned, and none were performed.

The Cochran-Mantel-Haenszel (CMH) test was used to compare the proportions between groups and estimate the treatment difference and its 95% confidence interval for in-hospital mortality, mortality on days 90, 180, 365 and 456, occurrence of a new hospitalization and occurrence of SARS-CoV-2 reinfection between discharge from the index hospitalization and days 90, 180, 365 and 456 (CMH test stratified according to vaccination status: initiated yes or no). For safety analyses, the number of participants with at least one adverse event (AE), with at least one grade 3 or 4 AE, and with at least one serious adverse event were compared between groups using a stratified CMH test. Two-sided p-values were reported but not corrected for multiplicity.

More details on the statistical methods are provided in appendix. The analyses were performed using SAS software version 9.4.

Results

Due to declining enrolment rates and *in-vitro* data suggesting decreased activity of AZD7442 against the omicron circulating variants,[12,13] the study steering committee decided to stop the inclusions at all participating sites on July 1, 2022, before reaching the targeted sample size.

Between April 28, 2021, and June 23, 2022, 237 participants were randomized to AZD7442 (N=127) or placebo (N=110) and 226 actually received the allocated intervention (AZD7442 N=123 and placebo N=103) (Figure 1). The numbers of participants included in the different analyses are shown in Figure 1. Serum samples were obtained for 23.9% of participants (54/226) on the last outpatient visit on day 365, and the last phone call on day 456 was performed for 66.8% of participants (151/226) (Supplementary Table S1).

Baseline characteristics are reported in table 1. The median age was 66 years (IQR 53-76); 68.6% (155/226) of participants were male, and 77% (174/226) had at least one comorbidity. The median number of days between symptom onset and randomization was 7 (IQR 6–9). Most participants had a positive SARS-CoV-2 serology at inclusion (65.6%, 145/226), and vaccination had been initiated for 45.1% (102/226). Most participants were infected with a 'pre-Omicron' variant (58.8%, 133/226), 23.5% (53/226) were infected with Omicron BA.1, 9.7% (22/226) with Omicron BA.2 or BA.5, and 8% (18/226) had missing data.

There was no significant difference in the distribution of the 7-point ordinal scale between the AZD7442 and placebo groups, either at day 15 (primary endpoint) – OR=0.93 [0.54-1.61], P=0.81, antigen-positive mITT population; OR=0.85 [0.52-1.37], P=0.50, global mITT population – or at any other time point (Table 2). Significantly more rehospitalizations occurred between discharge and day 456 among participants who received AZD7442 in the global mITT population (OR=2.04 [1.03-4.05], P=0.04), but not in the antigen-positive mITT population (OR=1.78 [0.80-3.94], P=0.15). No significant differences were observed in mortality or SARS-CoV-2 reinfection.

Safety outcomes are shown in Table 3. In the AZD7442 group, 52.8% (65/123) of participants experienced at least one adverse event (AE), compared to 52.4% (54/103) in the placebo group (P=0.97). At least one grade 3 or 4 AE occurred in 35.8% (44/123) of participants in the AZD7442 group, versus 38.8% (40/103) in the placebo group (P=0.56). Serious adverse events were reported in 35.0% (43/123) of participants in the AZD7442 group, compared to 38.8% (40/103) in the placebo group (P=0.48).

Regarding the immunogenicity analyses, 156 participants had a non-missing baseline anti-drug antibody (ADA) result and at least one non-missing post-baseline result (Table 4). In the AZD7442 treatment group, 13/87 participants (14.9%) developed ADA to AZD7442 versus 8/69 (11.6%) in the placebo group, including 12/87 (13.8%) that were classified as treatment-emergent ADA ~~(TE-ADA), versus compared to 8/69 (11.6%) ADA positive and~~ 5/69 (7.2%) ~~TE-ADA positive participants~~ in the placebo group (OR=2.02 [0.66-6.14], P=0.21).

AZD7442 serum concentrations were detectable up to day 365 for 100% of sampled participants (35/35), with a mean (SD) concentration of 183.2 (99.2) µg/mL at the end of infusion, 86.7 (25.6) µg/mL on day 8, 33.2 (13.5) µg/mL on day 90, and 4.2 (2.4) µg/mL on day 365. AZD7442 concentration-time profiles were similar between TE-ADA positive and ADA-negative participants, although no statistical test was performed (Figure 2, supplementary table S6).

The neutralizing activity (log10 ID50) against the Delta variant was significantly different between treatment groups on days 29 ($P<10^{-17}$), 90 ($P<10^{-18}$), and 180 ($P<10^{-4}$), but not on day 365 (P=0.71) (Figure 3 and supplementary Table S7). A post-hoc analysis using a linear mixed-effects model to account for repeated measurements provided concordant results

(Supplementary table S9). Neutralizing activity against the variant of infection and subgroup analyses are presented in appendix.

Discussion

To our knowledge, this is the first study to report the pharmacokinetics and immunogenicity of AZD7442 in hospitalized COVID-19 patients with long-term follow-up. No significant differences were observed between treatment groups in clinical status, mortality, or SARS-CoV-2 reinfection. Rehospitalizations between discharge and day 456 appeared more frequent among participants who received AZD7442 in the global mITT population, but the difference was weakly significant (P=0.04) and was not observed in the antigen-positive mITT population. ~~Given the number of statistical tests performed without adjustment for multiplicity, this finding is likely a spurious association.~~ Safety profiles were similar between AZD7442 and placebo groups, with no differences in adverse events, serious adverse events, or grade 3 or 4 adverse events.

All biologics, including human mAbs, may promote unwanted immune responses, ranging from transient appearance of anti-drug antibodies (ADA) without any clinical significance, to severe life-threatening conditions such as anaphylaxis.[14] Immunogenicity analyses showed that 14.9% of AZD7442-treated participants developed ADA, with more than 90% of these cases classified as TE-ADA (13.8% of AZD7442-treated participants). Nearly 12% of participants receiving placebo also developed ADA, with 62% of these cases classified as TE-ADA (7.2% of the placebo group). This is consistent with findings from previous studies on AZD7442, where the

development of TE-ADA was observed in patients who received AZD7442, but also in patients who received placebo, varying from 2% in healthy individuals[1,15] to 17% in other patient populations across pivotal randomized controlled trials.[5,6]

Drug concentrations declined over time but remained detectable at day 365 for all sampled participants. ADA positivity status did not seem to impact the concentration-time profiles of AZD7442, although no statistical test was performed. Our findings are consistent with results from other AZD7442 trials (PROVENT, STORM CHASER and TACKLE),[5,6] which also showed that serum concentration-time profiles were similar in participants with or without TE-ADA, indicating no apparent effect of ADA on the pharmacokinetics of AZD7442.

Neutralizing antibodies against the Delta variant were significantly higher in the AZD7442 group compared to placebo up to day 180, regardless of the vaccination or serology status (assessed up to day 90). Although the difference in neutralizing activity was no longer significant on day 365, the observed sustained neutralizing activity up to six months, provide important insights into the immune responses elicited by AZD7442, which may be useful for the future development of long-acting monoclonal antibodies.

One of the key strengths of this study is its robust design as a phase 3, randomized, double-blind, multicenter trial with a large population and long-term follow-up. The rigorous assessment of both clinical and immunological endpoints allows for a comprehensive evaluation of AZD7442's effects. Additionally, the detailed immunogenicity analyses provide valuable information on the development of ADA and their potential impact on pharmacokinetics.

However, several limitations should be acknowledged. First, due to a premature discontinuation of inclusions, the study was not powered to detect small differences in long-term clinical outcomes, which may have influenced our ability to identify potential benefits of AZD7442. Second, while neutralizing antibody titres were significantly higher in the AZD7442 group, the clinical implications of this immune response to protect against an acute infection remain uncertain, particularly in the context of emerging SARS-CoV-2 variants. Third, the proportion of vaccinated participants was relatively high (45.1%), which may have influenced the observed immune responses and limited the ability to detect potentially additional benefits in an unvaccinated population as compared to the ACTIV-3-therapeutics for inpatients with COVID-19 (TICO) study, which included 1417 patients, 73% of whom were unvaccinated.[4] Finally, enrolment was restricted to a single European region, which may limit the generalizability of the results. No adjustment for multiplicity of statistical tests was performed, therefore results must be interpreted accordingly.

In this trial, AZD7442 did not demonstrate any clinical benefit or safety concerns up to 15 months. This study also provides valuable data on the pharmacokinetics, immunogenicity, and neutralizing activity of AZD7442 in hospitalized COVID-19 patients.

Tables

Table 1. Baseline characteristics of participants in the global modified intention-to-treat population.

	Overall (N=226)	AZD7442 (N=123)	Placebo (N=103)
Median age, years	66.0 [53.0-76.0]	64.0 [53.0-76.0]	68.0 [52.0-76.0]
Sex male,	155 (68.6%)	78 (63.4%)	77 (74.8%)
Number of comorbidities*			
0	52 (23.0%)	28 (22.8%)	24 (23.3%)
1	71 (31.4%)	38 (30.9%)	33 (32.0%)
2	50 (22.1%)	27 (22.0%)	23 (22.3%)
3	32 (14.2%)	18 (14.6%)	14 (13.6%)
>3	21 (9.3%)	12 (9.8%)	9 (8.7%)
Coexisting condition*[a]			
Chronic cardiac disease	72 (31.9%)	43 (35.0%)	29 (28.2%)
Obesity (BMI >= 30)	63 (27.9%)	38 (30.9%)	25 (24.3%)
Diabetes	58 (25.7%)	37 (30.1%)	21 (20.4%)
Current smoker	15 (48.4%)	7 (46.7%)	8 (50.0%)
Chronic pulmonary disease (including asthma)	53 (23.5%)	27 (22.0%)	26 (25.2%)
Active cancer (including hematological malignancy)	30 (13.3%)	12 (9.8%)	18 (17.5%)
Median days from symptoms onset and random assignment*	7.0 [6.0-9.0]	8.0 [6.0-9.0]	7.0 [5.0-9.0]
NEWS2 Score*	7.0 [5.0-9.0]	7.0 [5.0-8.0]	6.0 [5.0-9.0]
Clinical status (7-point WHO ordinal scale)			
3. Hospitalised, not requiring supplemental oxygen	9 (4.0%)	6 (4.9%)	3 (2.9%)
4. Hospitalised, requiring supplemental oxygen	179 (79.2%)	93 (75.6%)	86 (83.5%)
5. Hospitalised, on non-invasive ventilation or high flow oxygen devices	38 (16.8%)	24 (19.5%)	14 (13.6%)
Randomization site			
Intensive care unit	32 (14.2%)	21 (17.1%)	11 (10.7%)
Conventional unit	194 (85.8%)	102 (82.9%)	92 (89.3%)
Vaccination initiation (partly or fully)	102 (45.1%)	56 (45.5%)	46 (44.7%)
Serology*			
Negative (Anti-N antibodies - and Anti-S RBD antibodies -)	76 (34.4%)	44 (36.4%)	32 (32.0%)
Positive (Anti-N antibodies + or Anti-S RBD antibodies +)	145 (65.6%)	77 (63.6%)	68 (68.0%)
Variant of infection*[b]			
Pre-Omicron	133 (58.8%)	70 (56.9%)	63 (61.2%)
Omicron BA1	53 (23.5%)	32 (26.0%)	21 (20.4%)
Omicron BA2/5	22 (9.7%)	11 (8.9%)	11 (10.7%)
Unknown	18 (8.0%)	10 (8.1%)	8 (7.8%)
Median normalised viral load in nasopharyngeal swabs at baseline (log_{10} copies per 10000 cells)[c]	4.0 [2.5--5.2]	3.9 [2.4-5.1]	4.1 [2.7-5.3]

Data are median [IQR] or n (%).

* Denotes variables with missing data: current smoker (N=3), serology (N=5), body weight (N=11); NEWS2 Score (N=20).

[a] Only conditions with a relative frequency greater than 10% are displayed in the table.

[b] Sequencing data for variant of infection was missing at baseline for 71 participants. It was imputed using available sequencing data on days 3 or 8. If no sequencing data was available, the variant of infection was imputed to be the variant that was dominant in France at the time of the patient's symptoms onset, according to epidemiological surveys.

[c] Undetectable viral load values (i.e. values < 1 log10 copies/10 000 cells) were imputed to 0.7 log10 copies/10 000 cells.

Table 2. Clinical endpoints in the antigen positive and global modified intention to treat populations, overall and according to the treatment group.

	Antigen positive (N=173)				Global (N=226)			
	Overall (N=173)	**AZD7442 (N=91)**	**Placebo (N=82)**	**AZD7442 vs. Placebo Effect measure (95%CI)**	**Overall (N=226)**	**AZD7442 (N=123)**	**Placebo (N=103)**	**AZD7442 vs. Placebo Effect measure (95%CI)**
7-point ordinal scale on day 15*								
1. Not hospitalized, no limitations on activities	35 (20.2%)	15 (16.5%)	20 (24.4%)		48 (21.2%)	20 (16.3%)	28 (27.2%)	
2. Not hospitalized, limitation on activities	77 (44.5%)	45 (49.5%)	32 (39.0%)		104 (46.0%)	63 (51.2%)	41 (39.8%)	
3. Hospitalized, not requiring supplemental oxygen	18 (10.4%)	9 (9.9%)	9 (11.0%)		24 (10.6%)	14 (11.4%)	10 (9.7%)	
4. Hospitalized, requiring supplemental oxygen	9 (5.2%)	7 (7.7%)	2 (2.4%)	OR=0.93 (0.54 to 1.61) [P=0.81]	13 (5.8%)	10 (8.1%)	3 (2.9%)	OR=0.85 (0.52 to 1.37) [P=0.50]
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	6 (3.5%)	2 (2.2%)	4 (4.9%)		7 (3.1%)	2 (1.6%)	5 (4.9%)	
6. Hospitalized, on invasive mechanical ventilation or ECMO	11 (6.4%)	5 (5.5%)	6 (7.3%)		12 (5.3%)	6 (4.9%)	6 (5.8%)	
7. Death	17 (9.8%)	8 (8.8%)	9 (11.0%)		18 (8.0%)	8 (6.5%)	10 (9.7%)	
7-point ordinal scale on day 365								
1. Not hospitalized, no limitations on activities	100 (57.8%)	50 (54.9%)	50 (61.0%)		135 (59.7%)	72 (58.5%)	63 (61.2%)	
2. Not hospitalized, limitation on activities	35 (20.2%)	21 (23.1%)	14 (17.1%)		47 (20.8%)	29 (23.6%)	18 (17.5%)	
3. Hospitalized, not requiring supplemental oxygen	5 (2.9%)	4 (4.4%)	1 (1.2%)	OR=0.89 (0.49 to 1.61) [P=0.70]	6 (2.7%)	4 (3.3%)	2 (1.9%)	OR=1.05 (0.62 to 1.78) [P=0.85]
4. Hospitalized, requiring supplemental oxygen	1 (0.6%)	1 (1.1%)	0 (0.0%)		1 (0.4%)	1 (0.8%)	0 (0.0%)	
7. Death	32 (18.5%)	15 (16.5%)	17 (20.7%)		37 (16.4%)	17 (13.8%)	20 (19.4%)	
In hospital mortality	21 (12.1%)	9 (9.9%)	12 (14.6%)	OR=0.64 (0.25 to 1.61) [P=0.34]	23 (10.2%)	9 (7.3%)	14 (13.6%)	OR=0.49 (0.20 to 1.19) [P=0.11]
Mortality on day 456	33 (19.1%)	16 (17.6%)	17 (20.7%)	OR=0.80 (0.36 to 1.78) [P=0.59]	39 (17.3%)	19 (15.4%)	20 (19.4%)	OR=0.72 (0.35 to 1.50) [P=0.39]
Occurrence of new hospitalization between discharge from index hospital and day 456	33 (19.1%)	21 (23.1%)	12 (14.6%)	OR=1.78 (0.80 to 3.94) [P=0.15]	49 (21.7%)	33 (26.8%)	16 (15.5%)	OR=2.04 (1.03 to 4.05) [P=0.04]
Confirmed SARS-CoV-2 reinfection between discharge from index hospital and day 456	22 (19.5%)	12 (19.7%)	10 (19.2%)	OR=1.03 (0.40 to 2.62) [P=0.95]	29 (19.1%)	17 (19.3%)	12 (18.8%)	OR=1.04 (0.46 to 2.35) [P=0.93]

Data are n (%).

* Data for the 7-point ordinal scale on day 15 (primary endpoint) was missing for 11 participants in the AZD7442 group and 13 participants in the placebo group. Missing data for the other endpoints are reported in Supplementary Table S3.

Table 3. Summary of the number of patients with at least one adverse event, serious adverse event, disease-related event, through day 456 in the global safety population, overall and according to the treatment group. Some patients had more than one adverse event (AE) or serious adverse event (SAE). AEs and SAEs do not include disease-related events (DREs).

	Global mITT (N=226)	AZD7442 (N=123)	Placebo (N=103)	AZD7442 vs. Placebo Effect measure (95% CI)
Number of patients with:				
Any adverse events	119 (52.7%)	65 (52.8%)	54 (52.4%)	OR=0.99 (0.58 to 1.69) [P=0.97]
Any grade 1 adverse events	24 (10.6%)	13 (10.6%)	11 (10.7%)	
Any grade 2 adverse events	35 (15.5%)	23 (18.7%)	12 (11.7%)	
Any grade 3 adverse events	53 (23.5%)	30 (24.4%)	23 (22.3%)	
Any grade 4 adverse events	47 (20.8%)	23 (18.7%)	24 (23.3%)	
Any grade 1 and 2 adverse events	52 (23.0%)	30 (24.4%)	22 (21.4%)	
Any grade 3 and 4 adverse events	84 (37.2%)	44 (35.8%)	40 (38.8%)	OR=0.84 (0.48 to 1.48) [P=0.56]
Any disease-related events	55 (24.3%)	28 (22.8%)	27 (26.2%)	
Any disease-related events with fatal outcome	11 (4.9%)	5 (4.1%)	6 (5.8%)	
Any serious adverse events	83 (36.7%)	43 (35.0%)	40 (38.8%)	OR=0.82 (0.46 to 1.44) [P=0.48]
Any serious adverse events related to AZD7442 or placebo	21 (9.3%)	11 (8.9%)	10 (9.7%)	
Any serious adverse events leading to outcome of death	28 (12.4%)	14 (11.4%)	14 (13.6%)	

Data are n (%).

Table 4. Antidrug antibody positivity to tixagevimab, cilgavimab, or AZD7442 through day 365.

ADA: antidrug antibody. TE-ADA: Treatment-emergent ADA.
TE-ADA positive: treatment-induced (negative at baseline and at least one positive result post-baseline) or treatment-boosted (baseline titre that increased by ≥ 4 times)
Non TE-ADA positive: ADA positive (titres ≥ 2 times the assay limit, i.e. 160 units for tixagevimab and 80 units for cilgavimab), but not meeting the criteria for TE-ADA positivity
ADA-negative: ADA negative at all times.

	ADA to tixagevimab			ADA to cilgavimab			ADA to AZD7442 [d]			
	Overall (N = 156)	AZD7442 (N = 87)	Placebo (N = 69)	Overall (N = 156)	AZD7442 (N = 87)	Placebo (N = 69)	Overall (N = 156)	AZD7442 (N = 87)	Placebo (N = 69)	AZD7442 vs. Placebo Effect measure (95% CI)
TE-ADA positive	13 (8.3%)	9 (10.3%)	4 (5.8%)	13 (8.3%)	10 (11.5%)	3 (4.3%)	17 (10.9%)	12 (13.8%)	5 (7.2%)	OR=2.02 (0.66 to 6.14) [P=0.21]
Non TE-ADA positive	4 (2.6%)	2 (2.3%)	2 (2.9%)	2 (1.3%)	1 (1.1%)	1 (1.4%)	4 (2.6%)	1 (1.1%)	3 (4.3%)	
ADA negative	139 (89.1%)	76 (87.4%)	63 (91.3%)	141 (90.4%)	76 (87.4%)	65 (94.2%)	135 (86.5%)	74 (85.1%)	61 (88.4%)	
Maximum ADA titres for TE-ADA positive participants	320 [160-640]	320 [160-320]	800 [240-1280]	320 [160-640]	240 [160-640]	320 [80-320]	320 [160-640]	320 [160-640]	320 [160-1280]	

Data are median [IQR] or n (%).

Figures

Figure 1. Flowchart. (ITT: intention to treat, ADA: anti-drug antibodies, PK: pharmacokinetics)

Figure 2. Evolution of AZD7442 serum concentrations (mean ± 95% CI) from baseline to day 365, according to ADA positivity status. Treatment-emergent anti-drug antibody (TE-ADA) positivity was defined as treatment-induced (negative at baseline and at least one positive result post-baseline) or treatment-boosted (baseline titre that increased by ≥ 4 times) positivity. ADA negativity was defined as being ADA negative at all times. All samples had detectable concentrations up to day 365.

Figure 3: Neutralizing activity (mean log10 ID50 ± 95% CI) against the Delta variant, from baseline to day 365, by treatment group.

Transparancy declaration

Conflict of interest disclosure

RG reports consulting fees from Celgene, Novartis, Roche, Bristol Myers Squibb, Takeda, Abbvie, AstraZeneca, Janssen, Merck Sharp & Dohme, Merck, Gilead, and Daiichi Sankvo; lecture fees from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Sandoz, Abbvie, Gilead, and Daiichi Sankvo; support for attending meetings from Roche, Amgen, Janssen, AstraZeneca, Novartis, Merck Sharp & Dohme, Celgene, Gilead, Bristol Myers Squibb, Abbvie, and Daiichi Sankvo; participation in a Data Safety and Monitoring Board for Celgene, Novartis, Roche, Bristol Myers Squibb, Takeda, Abbvie, AstraZeneca, Janssen, Merck Sharp & Dohme, Merck, Gilead, and Daiichi Sankyo; research grants from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Sandoz, Abbvie, Gilead, and Daiichi Sankyo. J-AP reports consulting fees from Pfizer, Merck Sharp & Dohme, and Janssen-Cilag; lecture fees from Pfizer; and support for attending meetings from Pfizer. DC reports grants and lecture fees from Janssen and lecture fees from Gilead, outside the submitted work. CB reports participation in a Data Safety and Monitoring Board for 4Living Biotech; and consulting fees from Da Volterra and Mylan Pharmaceuticals, outside the submitted work. FM reports grants and consulting fees from Da Volterra, grants from Sanofi, and consulting fees from Ipsen, outside the submitted work. MH reports grants from The Belgian Center for Knowledge (KCE), the Fonds Erasme-COVID-Université Libre de Bruxelles and the EU-Horizon programme, for the submitted work; and has received support for attending meetings from Pfizer; support for participation on an advisory board for therapeutics on COVID-19; and support for leadership for the Belgian guidelines on therapeutics for COVID-19 and acting as a treasurer for the Belgian Society of Clinical Microbiology and Infectious Diseases. All other authors decalre no competing interests.

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Access to data:

Upon publication, de-identified individual participant data underlying this Article, together with a data dictionary describing the dataset variables, will be made available to researchers whose proposed use has been approved by the DisCoVeRy Steering Committee. To request the dataset, please contact either the corresponding author or the sponsor's representative (INSERM) to obtain a data access form. All requests will be reviewed by the Trial Management Team and the DisCoVeRy Steering Committee. For approved requests, data will be shared following signature of a data transfer agreement with the study sponsor. The protocol and statistical analysis plan are available as supplementary material of this article. Other documents related to the study will be made available upon request.

Contribution:

FA, MH, CD, NPS, MBD, DC, YY, CB, CRM, and FM were involved in the design, establishment, and day-to-day management and implementation of the trial. FA, MH, CD, DC, YY and FM obtained funding for the trial. MH, SJ, FG, FD, JR, NdC, DG, ELL, KL, VT, EF, DM, TS, JC, FCR, AMDR, PL, GMB, CR, KA, VLM, LP, PS, XL, MT, PC, OD, SG, MG, PL, FVB, CV, LB, EBN, AC, AK, FL, ERN, SS, GT, NPS, FA included participants in the trial. MBD, AG, MAT, GD and LJ were responsible for the virological

analyses. PP and GC were responsible for the immunological analyses ; IB and SDD were involved in the seroneutralization analyses. ADi, NM, VTe were responsible of the safety monitoring and analyses. SCD, ADe, CD, HE, CFL, SlM, AM, and MN were in charge of trial promotion and data monitoring. ST, OK, NB, and BL were responsible for the biobanking. MH, JE, RG, EH, MHa, JAP, AP, JRB, TS, KT, MT, ST, SU, GC, ADi, MBD, HE, DC, YY, FM, and FA were voting members of the trial steering committee. THLH, CRM, NB, DB, JG, and FM were involved in the statistical analyses. CRM, FM, MH, and FA wrote the original draft of the manuscript, which was reviewed and edited by NPS, NM, AG, PP, GC, JG, and DC. MH, CRM, DB, NB, THLH, CD, CFL, ADe, and AM had full access to the blinded data. NB had full access to unblinded data. All authors contributed to refinement of and approved this manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Original article:

Efficacy, safety, pharmacokinetics, immunogenicity, and serum neutralizing activity of AZD7442 (tixagevimab-cilgavimab) in hospitalized COVID-19 patients: long-term results from the DisCoVeRy trial

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Abstract

Objectives. To report long-term clinical efficacy, safety, pharmacokinetics, immunogenicity and seroneutralization results of AZD7442 (monoclonal antibodies tixagevimab-cilgavimab) in hospitalized COVID-19 patients.

Methods. In this phase 3, double-blind, randomized, multicenter trial, hospitalized adults with PCR-confirmed SARS-CoV-2 infection were randomized 1:1 to receive AZD7442 or placebo, and followed-up until day 456, with repeated blood sample collections until day 365. Clinical endpoints included clinical status, mortality, rehospitalization, SARS-CoV-2 reinfection, and adverse events. Antidrug antibodies (ADA) and serum drug concentrations were measured. Analyses were performed on the modified intention-to-treat populations, defined as participants who actually received the intervention.

Results. Between April 28, 2021, and June 23, 2022, 237 participants were randomized to AZD7442 (n=127) or placebo (n=110), and 123 participants actually received AZD7442. Participants were infected with pre-Omicron variants in 58.8% (133/226) of cases, versus 33.2% (75/226) of Omicron BA1, BA2, or BA5, and 8% (18/226) missing data. There was no significant difference in the distribution of the 7-point ordinal scale between the AZD7442 and

placebo groups, either on day 15 (primary endpoint), OR=0.93 [0.54-1.61], P=0.81, or any other time point. Significantly more rehospitalizations occurred between discharge and day 456 among participants who received AZD7442 in the global mITT population (OR=2.04 [1.03-4.05], P=0.04), but not in the antigen-positive mITT population (OR=1.78 [0.80-3.94], P=0.15). No significant differences were observed in mortality, SARS-CoV-2 reinfection, or adverse events. In the AZD7442 group, 12/87 participants (13.8%) had treatment-emergent ADA versus 5/69 (7.2%) in the placebo group (OR=2.02 [0.66-6.14], P=0.21). Serum drug concentrations were detectable up to day 365 for all sampled participants (35/35). Neutralizing antibody titres were significantly higher in the AZD7442 group up to day 180.

Conclusions. AZD7442 did not demonstrate any clinical benefit and was safe up to 15 months. This study also provides valuable data on the pharmacokinetics, immunogenicity, and neutralizing activity of AZD7442 in hospitalized COVID-19 patients.

Introduction

AZD7442 is a cocktail of two monoclonal antibodies (mAbs), tixagevimab and cilgavimab, derived from B cells obtained from patients who had recovered from SARS-CoV2 infection.[1] The fragment crystallizable (Fc) regions of the two mAbs were engineered to extend serum half-life through the YTE modification (amino acid substitutions M252Y/S254T/T256E), and to improve safety by reducing the risk of antibody-dependent enhancement of disease through the TM modification (amino acid substitutions L234F/L235E/P331S).[1]

In the context of an innovative therapeutic agent to prevent or treat infectious diseases, with a theoretically extended half-life, data on long-term patient follow-up (up to 15 months post-administration of the drug) concerning efficacy, safety and pharmacokinetics of AZD7442 are essential. Such data have already been provided for healthy individuals, and adult patients at risk of progressing to severe COVID-19 disease, either uninfected or with confirmed mild-to-moderate COVID-19.[1–4] These studies confirmed that AZD7442 was well tolerated and had a favorable safety profile up to 15 months in all patient groups.[5,6] Furthermore, serum concentration-time profiles were consistently similar for the two mAbs, were not found to be influenced by the presence of treatment-emergent antidrug antibodies (ADA), and the measured half-life of AZD7442 was approximately 90 days in all patient groups, confirming the extended half-life of both mAbs. However, no such data have yet been provided for patients hospitalized with COVID-19 and treated with 600 mg of intravenous AZD7442.

The primary analyses of the DisCoVeRy trial were conducted once all participants had completed follow-up through day 90 and were published previously,[7,8] showing no benefit or harm of AZD7442 on any clinical, virological, or safety endpoints. We report here the long-term clinical efficacy, safety, pharmacokinetics, and immunogenicity results.

Materials and methods

Study design

DisCoVeRy is a phase 3, adaptive, multicenter, randomized, double-blind, superiority trial designed to evaluate the efficacy and safety of drugs for the treatment of adults hospitalized for COVID-19 (ClinicalTrials.gov NCT04315948). The first four interventions evaluated (lopinavir/ritonavir, lopinavir/ritonavir plus IFN-b-1a, hydroxychloroquine, and remdesivir) were discontinued for futility and the results reported elsewhere.[9–11] A protocol amendment (version 14) was approved on April 20th, 2021 to evaluate AZD7442, developed by AstraZeneca. The study was conducted across 63 sites in 13 European countries (Austria, Belgium, Czech Republic, France, Greece, Hungary, Ireland, Luxembourg, Norway, Poland, Portugal, Slovakia, and Spain). The trial was approved by the Ethics Committees in each country and was sponsored by the Institut national de la santé et de la recherche médicale (Inserm, France); it was conducted in accordance with the Declaration of Helsinki.

Participants

Eligible participants were adults (≥18 years) hospitalized with SARS-CoV-2 infection confirmed on a RT-PCR performed on a nasopharyngeal (NP) swab within the 5 days preceding randomization, and a time between onset of symptoms and randomization of less than 9 days (extended to 11 days from September 20th, 2021, protocol V15). Participants with prior receipt of investigational or licensed mAb or vaccine indicated for the prevention of SARS-CoV-2 infection or COVID-19 were excluded. From September 20th, 2021, inclusion of patients with initiated (one dose) or completed (two doses) vaccination was allowed in a proportion of 20% of enrolled participants, provided they would not receive an additional dose in the 30 days following hospital discharge. Full inclusion and exclusion criteria are detailed in the appendix.

Written informed consent was obtained from all participants or their legal representative prior to randomization.

Randomization and masking

Participants were randomly assigned in a 1:1 ratio to receive AZD7442 or placebo in addition to standard of care (SoC). The randomization was stratified by region, by antigenic status obtained from the result of a rapid antigen test on a NP swab at enrolment, and, with protocol V15, by vaccination status. Randomization was performed via an electronic Case Report Form and used computer-generated blocks of various sizes. Allocation was concealed from participants, care providers, outcome assessors, and data analysts.

Procedures and assessments

The participants received a single intravenous infusion of tixagevimab-cilgavimab (600 mg at a maximum infusion rate of 50 mg/minute) or matching placebo (a 0.9% saline solution, prepared by an unblinded pharmacist) within 24 hours following randomization. Participants could not be treated with other monoclonal or polyclonal antibodies directly targeting SARS-CoV-2 during the study. The standard of care could include corticosteroids, remdesivir, and other immunomodulatory agents, at the discretion of the physician.

Participants were assessed daily while hospitalized. Follow-up assessments were scheduled on days 29 and 90 as outpatient consultations for discharged participants; on days 180 and 365 as outpatient consultations for as many patients as possible provided the center had sufficient ressources, otherwise by phone; and on day 456 by phone for all participants.

Blood samples were collected at baseline, on days 3, 8, and 15 (only for hospitalized participants), and on days 29, 90, 180 and 365 (for participants with outpatient consultations).

Endpoints

We report here: the clinical status, measured on the 7-point ordinal scale of the WHO Master Protocol v3.0, on days 15 (primary endpoint), 180 and 365; the in-hospital mortality; the mortality on days 180, 365, and 456; the occurrence of a new hospitalization between discharge from the index hospitalization and days 180, 365, and 456; and occurrence of SARS-CoV-2 reinfection between discharge from the index hospitalization and days 180, 365, and 456. Safety endpoints were recorded until day 456 and included: adverse events (AEs grade 1 through 4), serious adverse events (SAEs), disease-related adverse events (DRE). The definitions of immunogenicity endpoints follow those used in previous publications.[5,6] Treatment-emergent anti-drug antibody (TE-ADA) positivity was defined as treatment-induced (negative at baseline and at least one positive result post-baseline) or treatment-boosted (baseline titre that increased by ≥ 4 times) positivity. ADA negativity was defined as being ADA negative at all times. AZD7442 serum concentration was defined as the sum of tixagevimab and cilgavimab concentrations. Neutralizing antibody titres were measured against the Delta variant and each participants' variant of infection, and were reported as the 50% inhibitory dilution (ID50). Details are in appendix.

Populations

Clinical efficacy analyses were performed on the modified intention-to-treat (mITT) population, defined as participants for whom the infusion of the allocated treatment was actually initiated, and analyzed in their assigned randomization group. The safety population included all randomized participants, analyzed in their actual treatment group. Each population set was further categorized based on the antigenic status, defining « antigen-positive » and « global » (i.e. antigen-positive and antigen-negative) mITT and safety populations.

Statistical analyses

The clinical status measured on the 7-point ordinal scale was analyzed using a proportional odds model. The study was powered to detect an odds ratio (OR) of 1.5 (an OR greater than 1 indicates superiority of the experimental treatment over the control for each ordinal scale category), with 90% power and a two-sided type I error of 0.05, for the primary endpoint. Accounting for 5% of non-evaluable patients, 620 patients per arm were required. No interim analyses for efficacy or futility were planned, and none were performed.

The Cochran-Mantel-Haenszel (CMH) test was used to compare the proportions between groups and estimate the treatment difference and its 95% confidence interval for in-hospital mortality, mortality on days 90, 180, 365 and 456, occurrence of a new hospitalization and occurrence of SARS-CoV-2 reinfection between discharge from the index hospitalization and days 90, 180, 365 and 456 (CMH test stratified according to vaccination status: initiated yes or no). For safety analyses, the number of participants with at least one adverse event (AE), with at least one grade 3 or 4 AE, and with at least one serious adverse event were compared between groups using a stratified CMH test. Two-sided p-values were reported but not corrected for multiplicity.

More details on the statistical methods are provided in appendix. The analyses were performed using SAS software version 9.4.

Results

Due to declining enrolment rates and *in-vitro* data suggesting decreased activity of AZD7442 against the omicron circulating variants,[12,13] the study steering committee decided to stop the inclusions at all participating sites on July 1, 2022, before reaching the targeted sample size.

Between April 28, 2021, and June 23, 2022, 237 participants were randomized to AZD7442 (N=127) or placebo (N=110) and 226 actually received the allocated intervention (AZD7442 N=123 and placebo N=103) (Figure 1). The numbers of participants included in the different analyses are shown in Figure 1. Serum samples were obtained for 23.9% of participants (54/226) on the last outpatient visit on day 365, and the last phone call on day 456 was performed for 66.8% of participants (151/226) (Supplementary Table S1).

Baseline characteristics are reported in table 1. The median age was 66 years (IQR 53-76); 68.6% (155/226) of participants were male, and 77% (174/226) had at least one comorbidity. The median number of days between symptom onset and randomization was 7 (IQR 6–9). Most participants had a positive SARS-CoV-2 serology at inclusion (65.6%, 145/226), and vaccination had been initiated for 45.1% (102/226). Most participants were infected with a 'pre-Omicron' variant (58.8%, 133/226), 23.5% (53/226) were infected with Omicron BA.1, 9.7% (22/226) with Omicron BA.2 or BA.5, and 8% (18/226) had missing data.

There was no significant difference in the distribution of the 7-point ordinal scale between the AZD7442 and placebo groups, either at day 15 (primary endpoint) – OR=0.93 [0.54-1.61], P=0.81, antigen-positive mITT population; OR=0.85 [0.52-1.37], P=0.50, global mITT population – or at any other time point (Table 2). Significantly more rehospitalizations occurred between discharge and day 456 among participants who received AZD7442 in the global mITT population (OR=2.04 [1.03-4.05], P=0.04), but not in the antigen-positive mITT population (OR=1.78 [0.80-3.94], P=0.15). No significant differences were observed in mortality or SARS-CoV-2 reinfection.

Safety outcomes are shown in Table 3. In the AZD7442 group, 52.8% (65/123) of participants experienced at least one adverse event (AE), compared to 52.4% (54/103) in the placebo group (P=0.97). At least one grade 3 or 4 AE occurred in 35.8% (44/123) of participants in the AZD7442 group, versus 38.8% (40/103) in the placebo group (P=0.56). Serious adverse events were reported in 35.0% (43/123) of participants in the AZD7442 group, compared to 38.8% (40/103) in the placebo group (P=0.48).

Regarding the immunogenicity analyses, 156 participants had a non-missing baseline anti-drug antibody (ADA) result and at least one non-missing post-baseline result (Table 4). In the AZD7442 treatment group, 13/87 participants (14.9%) developed ADA to AZD7442 versus 8/69 (11.6%) in the placebo group, including 12/87 (13.8%) that were classified as treatment-emergent ADA versus 5/69 (7.2%) in the placebo group (OR=2.02 [0.66-6.14], P=0.21).

AZD7442 serum concentrations were detectable up to day 365 for 100% of sampled participants (35/35), with a mean (SD) concentration of 183.2 (99.2) µg/mL at the end of infusion, 86.7 (25.6) µg/mL on day 8, 33.2 (13.5) µg/mL on day 90, and 4.2 (2.4) µg/mL on day 365. AZD7442 concentration-time profiles were similar between TE-ADA positive and ADA-negative participants, although no statistical test was performed (Figure 2, supplementary table S6).

The neutralizing activity (log10 ID50) against the Delta variant was significantly different between treatment groups on days 29 ($P<10^{-17}$), 90 ($P<10^{-18}$), and 180 ($P<10^{-4}$), but not on day 365 (P=0.71) (Figure 3 and supplementary Table S7). A post-hoc analysis using a linear mixed-effects model to account for repeated measurements provided concordant results

(Supplementary table S9). Neutralizing activity against the variant of infection and subgroup analyses are presented in appendix.

Discussion

To our knowledge, this is the first study to report the pharmacokinetics and immunogenicity of AZD7442 in hospitalized COVID-19 patients with long-term follow-up. No significant differences were observed between treatment groups in clinical status, mortality, or SARS-CoV-2 reinfection. Rehospitalizations between discharge and day 456 appeared more frequent among participants who received AZD7442 in the global mITT population, but the difference was weakly significant (P=0.04) and was not observed in the antigen-positive mITT population. Safety profiles were similar between AZD7442 and placebo groups, with no differences in adverse events, serious adverse events, or grade 3 or 4 adverse events.

All biologics, including human mAbs, may promote unwanted immune responses, ranging from transient appearance of anti-drug antibodies (ADA) without any clinical significance, to severe life-threatening conditions such as anaphylaxis.[14] Immunogenicity analyses showed that 14.9% of AZD7442-treated participants developed ADA, with more than 90% of these cases classified as TE-ADA (13.8% of AZD7442-treated participants). Nearly 12% of participants receiving placebo also developed ADA, with 62% of these cases classified as TE-ADA (7.2% of the placebo group). This is consistent with findings from previous studies on AZD7442, where the development of TE-ADA was observed in patients who received AZD7442, but also in patients

who received placebo, varying from 2% in healthy individuals[1,15] to 17% in other patient populations across pivotal randomized controlled trials.[5,6]

Drug concentrations declined over time but remained detectable at day 365 for all sampled participants. ADA positivity status did not seem to impact the concentration-time profiles of AZD7442, although no statistical test was performed. Our findings are consistent with results from other AZD7442 trials (PROVENT, STORM CHASER and TACKLE),[5,6] which also showed that serum concentration-time profiles were similar in participants with or without TE-ADA, indicating no apparent effect of ADA on the pharmacokinetics of AZD7442.

Neutralizing antibodies against the Delta variant were significantly higher in the AZD7442 group compared to placebo up to day 180, regardless of the vaccination or serology status (assessed up to day 90). Although the difference in neutralizing activity was no longer significant on day 365, the observed sustained neutralizing activity up to six months, provide important insights into the immune responses elicited by AZD7442, which may be useful for the future development of long-acting monoclonal antibodies.

One of the key strengths of this study is its robust design as a phase 3, randomized, double-blind, multicenter trial with a large population and long-term follow-up. The rigorous assessment of both clinical and immunological endpoints allows for a comprehensive evaluation of AZD7442's effects. Additionally, the detailed immunogenicity analyses provide valuable information on the development of ADA and their potential impact on pharmacokinetics.

However, several limitations should be acknowledged. First, due to a premature discontinuation of inclusions, the study was not powered to detect small differences in long-term clinical outcomes, which may have influenced our ability to identify potential benefits of AZD7442. Second, while neutralizing antibody titres were significantly higher in the AZD7442 group, the clinical implications of this immune response to protect against an acute infection remain uncertain, particularly in the context of emerging SARS-CoV-2 variants. Third, the proportion of vaccinated participants was relatively high (45.1%), which may have influenced the observed immune responses and limited the ability to detect potentially additional benefits in an unvaccinated population as compared to the ACTIV-3-therapeutics for inpatients with COVID-19 (TICO) study, which included 1417 patients, 73% of whom were unvaccinated.[4] Finally, enrolment was restricted to a single European region, which may limit the generalizability of the results. No adjustment for multiplicity of statistical tests was performed, therefore results must be interpreted accordingly.

In this trial, AZD7442 did not demonstrate any clinical benefit or safety concerns up to 15 months. This study also provides valuable data on the pharmacokinetics, immunogenicity, and neutralizing activity of AZD7442 in hospitalized COVID-19 patients.

Tables

Table 1. Baseline characteristics of participants in the global modified intention-to-treat population.

	Overall (N=226)	AZD7442 (N=123)	Placebo (N=103)
Median age, years	66.0 [53.0-76.0]	64.0 [53.0-76.0]	68.0 [52.0-76.0]
Sex male,	155 (68.6%)	78 (63.4%)	77 (74.8%)
Number of comorbidities*			
0	52 (23.0%)	28 (22.8%)	24 (23.3%)
1	71 (31.4%)	38 (30.9%)	33 (32.0%)
2	50 (22.1%)	27 (22.0%)	23 (22.3%)
3	32 (14.2%)	18 (14.6%)	14 (13.6%)
>3	21 (9.3%)	12 (9.8%)	9 (8.7%)
Coexisting condition*[a]			
Chronic cardiac disease	72 (31.9%)	43 (35.0%)	29 (28.2%)
Obesity (BMI >= 30)	63 (27.9%)	38 (30.9%)	25 (24.3%)
Diabetes	58 (25.7%)	37 (30.1%)	21 (20.4%)
Current smoker	15 (48.4%)	7 (46.7%)	8 (50.0%)
Chronic pulmonary disease (including asthma)	53 (23.5%)	27 (22.0%)	26 (25.2%)
Active cancer (including hematological malignancy)	30 (13.3%)	12 (9.8%)	18 (17.5%)
Median days from symptoms onset and random assignment*	7.0 [6.0-9.0]	8.0 [6.0-9.0]	7.0 [5.0-9.0]
NEWS2 Score*	7.0 [5.0-9.0]	7.0 [5.0-8.0]	6.0 [5.0-9.0]
Clinical status (7-point WHO ordinal scale)			
3. Hospitalised, not requiring supplemental oxygen	9 (4.0%)	6 (4.9%)	3 (2.9%)
4. Hospitalised, requiring supplemental oxygen	179 (79.2%)	93 (75.6%)	86 (83.5%)
5. Hospitalised, on non-invasive ventilation or high flow oxygen devices	38 (16.8%)	24 (19.5%)	14 (13.6%)
Randomization site			
Intensive care unit	32 (14.2%)	21 (17.1%)	11 (10.7%)
Conventional unit	194 (85.8%)	102 (82.9%)	92 (89.3%)
Vaccination initiation (partly or fully)	102 (45.1%)	56 (45.5%)	46 (44.7%)
Serology*			
Negative (Anti-N antibodies - and Anti-S RBD antibodies -)	76 (34.4%)	44 (36.4%)	32 (32.0%)
Positive (Anti-N antibodies + or Anti-S RBD antibodies +)	145 (65.6%)	77 (63.6%)	68 (68.0%)
Variant of infection*[b]			
Pre-Omicron	133 (58.8%)	70 (56.9%)	63 (61.2%)
Omicron BA1	53 (23.5%)	32 (26.0%)	21 (20.4%)
Omicron BA2/5	22 (9.7%)	11 (8.9%)	11 (10.7%)
Unknown	18 (8.0%)	10 (8.1%)	8 (7.8%)
Median normalised viral load in nasopharyngeal swabs at baseline (log_{10} copies per 10000 cells)[c]	4.0 [2.5--5.2]	3.9 [2.4-5.1]	4.1 [2.7-5.3]

Data are median [IQR] or n (%).

* Denotes variables with missing data: current smoker (N=3), serology (N=5), body weight (N=11); NEWS2 Score (N=20).

[a] Only conditions with a relative frequency greater than 10% are displayed in the table.

[b] Sequencing data for variant of infection was missing at baseline for 71 participants. It was imputed using available sequencing data on days 3 or 8. If no sequencing data was available, the variant of infection was imputed to be the variant that was dominant in France at the time of the patient's symptoms onset, according to epidemiological surveys.

[c] Undetectable viral load values (i.e. values < 1 log10 copies/10 000 cells) were imputed to 0.7 log10 copies/10 000 cells.

Table 2. Clinical endpoints in the antigen positive and global modified intention to treat populations, overall and according to the treatment group.

	Antigen positive (N=173)				Global (N=226)			
	Overall (N=173)	**AZD7442 (N=91)**	**Placebo (N=82)**	**AZD7442 vs. Placebo Effect measure (95%CI)**	**Overall (N=226)**	**AZD7442 (N=123)**	**Placebo (N=103)**	**AZD7442 vs. Placebo Effect measure (95%CI)**
7-point ordinal scale on day 15*								
1. Not hospitalized, no limitations on activities	35 (20.2%)	15 (16.5%)	20 (24.4%)		48 (21.2%)	20 (16.3%)	28 (27.2%)	
2. Not hospitalized, limitation on activities	77 (44.5%)	45 (49.5%)	32 (39.0%)		104 (46.0%)	63 (51.2%)	41 (39.8%)	
3. Hospitalized, not requiring supplemental oxygen	18 (10.4%)	9 (9.9%)	9 (11.0%)		24 (10.6%)	14 (11.4%)	10 (9.7%)	
4. Hospitalized, requiring supplemental oxygen	9 (5.2%)	7 (7.7%)	2 (2.4%)	OR=0.93 (0.54 to 1.61) [P=0.81]	13 (5.8%)	10 (8.1%)	3 (2.9%)	OR=0.85 (0.52 to 1.37) [P=0.50]
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	6 (3.5%)	2 (2.2%)	4 (4.9%)		7 (3.1%)	2 (1.6%)	5 (4.9%)	
6. Hospitalized, on invasive mechanical ventilation or ECMO	11 (6.4%)	5 (5.5%)	6 (7.3%)		12 (5.3%)	6 (4.9%)	6 (5.8%)	
7. Death	17 (9.8%)	8 (8.8%)	9 (11.0%)		18 (8.0%)	8 (6.5%)	10 (9.7%)	
7-point ordinal scale on day 365								
1. Not hospitalized, no limitations on activities	100 (57.8%)	50 (54.9%)	50 (61.0%)		135 (59.7%)	72 (58.5%)	63 (61.2%)	
2. Not hospitalized, limitation on activities	35 (20.2%)	21 (23.1%)	14 (17.1%)		47 (20.8%)	29 (23.6%)	18 (17.5%)	
3. Hospitalized, not requiring supplemental oxygen	5 (2.9%)	4 (4.4%)	1 (1.2%)	OR=0.89 (0.49 to 1.61) [P=0.70]	6 (2.7%)	4 (3.3%)	2 (1.9%)	OR=1.05 (0.62 to 1.78) [P=0.85]
4. Hospitalized, requiring supplemental oxygen	1 (0.6%)	1 (1.1%)	0 (0.0%)		1 (0.4%)	1 (0.8%)	0 (0.0%)	
7. Death	32 (18.5%)	15 (16.5%)	17 (20.7%)		37 (16.4%)	17 (13.8%)	20 (19.4%)	
In hospital mortality	21 (12.1%)	9 (9.9%)	12 (14.6%)	OR=0.64 (0.25 to 1.61) [P=0.34]	23 (10.2%)	9 (7.3%)	14 (13.6%)	OR=0.49 (0.20 to 1.19) [P=0.11]
Mortality on day 456	33 (19.1%)	16 (17.6%)	17 (20.7%)	OR=0.80 (0.36 to 1.78) [P=0.59]	39 (17.3%)	19 (15.4%)	20 (19.4%)	OR=0.72 (0.35 to 1.50) [P=0.39]
Occurrence of new hospitalization between discharge from index hospital and day 456	33 (19.1%)	21 (23.1%)	12 (14.6%)	OR=1.78 (0.80 to 3.94) [P=0.15]	49 (21.7%)	33 (26.8%)	16 (15.5%)	OR=2.04 (1.03 to 4.05) [P=0.04]
Confirmed SARS-CoV-2 reinfection between discharge from index hospital and day 456	22 (19.5%)	12 (19.7%)	10 (19.2%)	OR=1.03 (0.40 to 2.62) [P=0.95]	29 (19.1%)	17 (19.3%)	12 (18.8%)	OR=1.04 (0.46 to 2.35) [P=0.93]

Data are n (%).

* Data for the 7-point ordinal scale on day 15 (primary endpoint) was missing for 11 participants in the AZD7442 group and 13 participants in the placebo group. Missing data for the other endpoints are reported in Supplementary Table S3.

Table 3. Summary of the number of patients with at least one adverse event, serious adverse event, disease-related event, through day 456 in the global safety population, overall and according to the treatment group. Some patients had more than one adverse event (AE) or serious adverse event (SAE). AEs and SAEs do not include disease-related events (DREs).

	Global mITT (N=226)	AZD7442 (N=123)	Placebo (N=103)	AZD7442 vs. Placebo Effect measure (95% CI)
Number of patients with:				
Any adverse events	119 (52.7%)	65 (52.8%)	54 (52.4%)	OR=0.99 (0.58 to 1.69) [P=0.97]
Any grade 1 adverse events	24 (10.6%)	13 (10.6%)	11 (10.7%)	
Any grade 2 adverse events	35 (15.5%)	23 (18.7%)	12 (11.7%)	
Any grade 3 adverse events	53 (23.5%)	30 (24.4%)	23 (22.3%)	
Any grade 4 adverse events	47 (20.8%)	23 (18.7%)	24 (23.3%)	
Any grade 1 and 2 adverse events	52 (23.0%)	30 (24.4%)	22 (21.4%)	
Any grade 3 and 4 adverse events	84 (37.2%)	44 (35.8%)	40 (38.8%)	OR=0.84 (0.48 to 1.48) [P=0.56]
Any disease-related events	55 (24.3%)	28 (22.8%)	27 (26.2%)	
Any disease-related events with fatal outcome	11 (4.9%)	5 (4.1%)	6 (5.8%)	
Any serious adverse events	83 (36.7%)	43 (35.0%)	40 (38.8%)	OR=0.82 (0.46 to 1.44) [P=0.48]
Any serious adverse events related to AZD7442 or placebo	21 (9.3%)	11 (8.9%)	10 (9.7%)	
Any serious adverse events leading to outcome of death	28 (12.4%)	14 (11.4%)	14 (13.6%)	

Data are n (%).

Table 4. Antidrug antibody positivity to tixagevimab, cilgavimab, or AZD7442 through day 365.

ADA: antidrug antibody. TE-ADA: Treatment-emergent ADA.
TE-ADA positive: treatment-induced (negative at baseline and at least one positive result post-baseline) or treatment-boosted (baseline titre that increased by ≥ 4 times)
Non TE-ADA positive: ADA positive (titres ≥ 2 times the assay limit, i.e. 160 units for tixagevimab and 80 units for cilgavimab), but not meeting the criteria for TE-ADA positivity
ADA-negative: ADA negative at all times.

	ADA to tixagevimab			ADA to cilgavimab			ADA to AZD7442 [d]			
	Overall (N = 156)	AZD7442 (N = 87)	Placebo (N = 69)	Overall (N = 156)	AZD7442 (N = 87)	Placebo (N = 69)	Overall (N = 156)	AZD7442 (N = 87)	Placebo (N = 69)	AZD7442 vs. Placebo Effect measure (95% CI)
TE-ADA positive	13 (8.3%)	9 (10.3%)	4 (5.8%)	13 (8.3%)	10 (11.5%)	3 (4.3%)	17 (10.9%)	12 (13.8%)	5 (7.2%)	OR=2.02 (0.66 to 6.14) [P=0.21]
Non TE-ADA positive	4 (2.6%)	2 (2.3%)	2 (2.9%)	2 (1.3%)	1 (1.1%)	1 (1.4%)	4 (2.6%)	1 (1.1%)	3 (4.3%)	
ADA negative	139 (89.1%)	76 (87.4%)	63 (91.3%)	141 (90.4%)	76 (87.4%)	65 (94.2%)	135 (86.5%)	74 (85.1%)	61 (88.4%)	
Maximum ADA titres for TE-ADA positive participants	320 [160-640]	320 [160-320]	800 [240-1280]	320 [160-640]	240 [160-640]	320 [80-320]	320 [160-640]	320 [160-640]	320 [160-1280]	

Data are median [IQR] or n (%).

Figures

Figure 1. Flowchart. (ITT: intention to treat, ADA: anti-drug antibodies, PK: pharmacokinetics)

Figure 2. Evolution of AZD7442 serum concentrations (mean ± 95% CI) from baseline to day 365, according to ADA positivity status. Treatment-emergent anti-drug antibody (TE-ADA) positivity was defined as treatment-induced (negative at baseline and at least one positive result post-baseline) or treatment-boosted (baseline titre that increased by ≥ 4 times) positivity. ADA negativity was defined as being ADA negative at all times. All samples had detectable concentrations up to day 365.

Figure 3: Neutralizing activity (mean log10 ID50 ± 95% CI) against the Delta variant, from baseline to day 365, by treatment group.

Transparancy declaration

Conflict of interest disclosure

RG reports consulting fees from Celgene, Novartis, Roche, Bristol Myers Squibb, Takeda, Abbvie, AstraZeneca, Janssen, Merck Sharp & Dohme, Merck, Gilead, and Daiichi Sankvo; lecture fees from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Sandoz, Abbvie, Gilead, and Daiichi Sankvo; support for attending meetings from Roche, Amgen, Janssen, AstraZeneca, Novartis, Merck Sharp & Dohme, Celgene, Gilead, Bristol Myers Squibb, Abbvie, and Daiichi Sankvo; participation in a Data Safety and Monitoring Board for Celgene, Novartis, Roche, Bristol Myers Squibb, Takeda, Abbvie, AstraZeneca, Janssen, Merck Sharp & Dohme, Merck, Gilead, and Daiichi Sankyo; research grants from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Sandoz, Abbvie, Gilead, and Daiichi Sankyo. J-AP reports consulting fees from Pfizer, Merck Sharp & Dohme, and Janssen-Cilag; lecture fees from Pfizer; and support for attending meetings from Pfizer. DC reports grants and lecture fees from Janssen and lecture fees from Gilead, outside the submitted work. CB reports participation in a Data Safety and Monitoring Board for 4Living Biotech; and consulting fees from Da Volterra and Mylan Pharmaceuticals, outside the submitted work. FM reports grants and consulting fees from Da Volterra, grants from Sanofi, and consulting fees from Ipsen, outside the submitted work. MH reports grants from The Belgian Center for Knowledge (KCE), the Fonds Erasme-COVID-Université Libre de Bruxelles and the EU-Horizon programme, for the submitted work; and has received support for attending meetings from Pfizer; support for participation on an advisory board for therapeutics on COVID-19; and support for leadership for the Belgian guidelines on therapeutics for COVID-19 and acting as a treasurer for the Belgian Society of Clinical Microbiology and Infectious Diseases. All other authors decalre no competing interests.

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Acknowledegments:

We thank all participants who consented to enroll in the trial, as well as all study and site staff whose indispensable assistance made the conduct of the DisCoVeRy trial possible (all listed in the appendix).

Access to data:

Upon publication, de-identified individual participant data underlying this Article, together with a data dictionary describing the dataset variables, will be made available to researchers whose proposed use has been approved by the DisCoVeRy Steering Committee. To request the dataset, please contact either the corresponding author or the sponsor's representative (INSERM) to obtain a data access form. All requests will be reviewed by the Trial Management Team and the DisCoVeRy Steering Committee. For approved requests, data will be shared following signature of a data transfer agreement with the study sponsor. The protocol and statistical analysis plan are available as supplementary material of this article. Other documents related to the study will be made available upon request.

Contribution:

FA, MH, CD, NPS, MBD, DC, YY, CB, CRM, and FM were involved in the design, establishment, and day-to-day management and implementation of the trial. FA, MH, CD, DC, YY and FM obtained funding for the trial. MH, SJ, FG, FD, JR, NdC, DG, ELL, KL, VT, EF, DM, TS, JC, FCR, AMDR, PL, GMB, CR, KA, VLM, LP, PS, XL, MT, PC, OD, SG, MG, PL, FVB, CV, LB, EBN, AC, AK, FL, ERN, SS, GT, NPS, FA included participants in the trial. MBD, AG, MAT, GD and LJ were responsible for the virological

analyses. PP and GC were responsible for the immunological analyses ; IB and SDD were involved in the seroneutralization analyses. ADi, NM, VTe were responsible of the safety monitoring and analyses. SCD, ADe, CD, HE, CFL, SlM, AM, and MN were in charge of trial promotion and data monitoring. ST, OK, NB, and BL were responsible for the biobanking. MH, JE, RG, EH, MHa, JAP, AP, JRB, TS, KT, MT, ST, SU, GC, ADi, MBD, HE, DC, YY, FM, and FA were voting members of the trial steering committee. THLH, CRM, NB, DB, JG, and FM were involved in the statistical analyses. CRM, FM, MH, and FA wrote the original draft of the manuscript, which was reviewed and edited by NPS, NM, AG, PP, GC, JG, and DC. MH, CRM, DB, NB, THLH, CD, CFL, ADe, and AM had full access to the blinded data. NB had full access to unblinded data. All authors contributed to refinement of and approved this manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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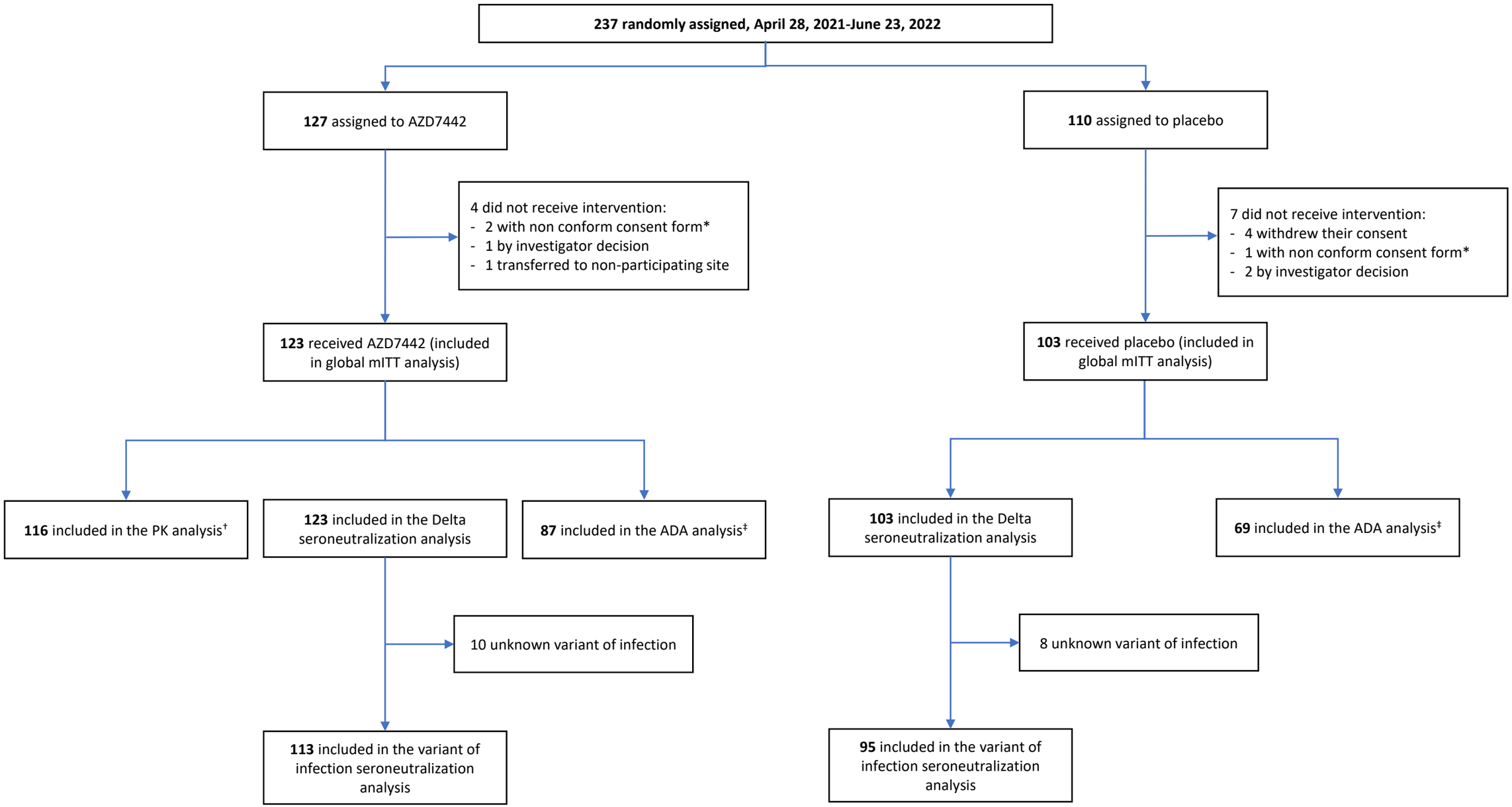
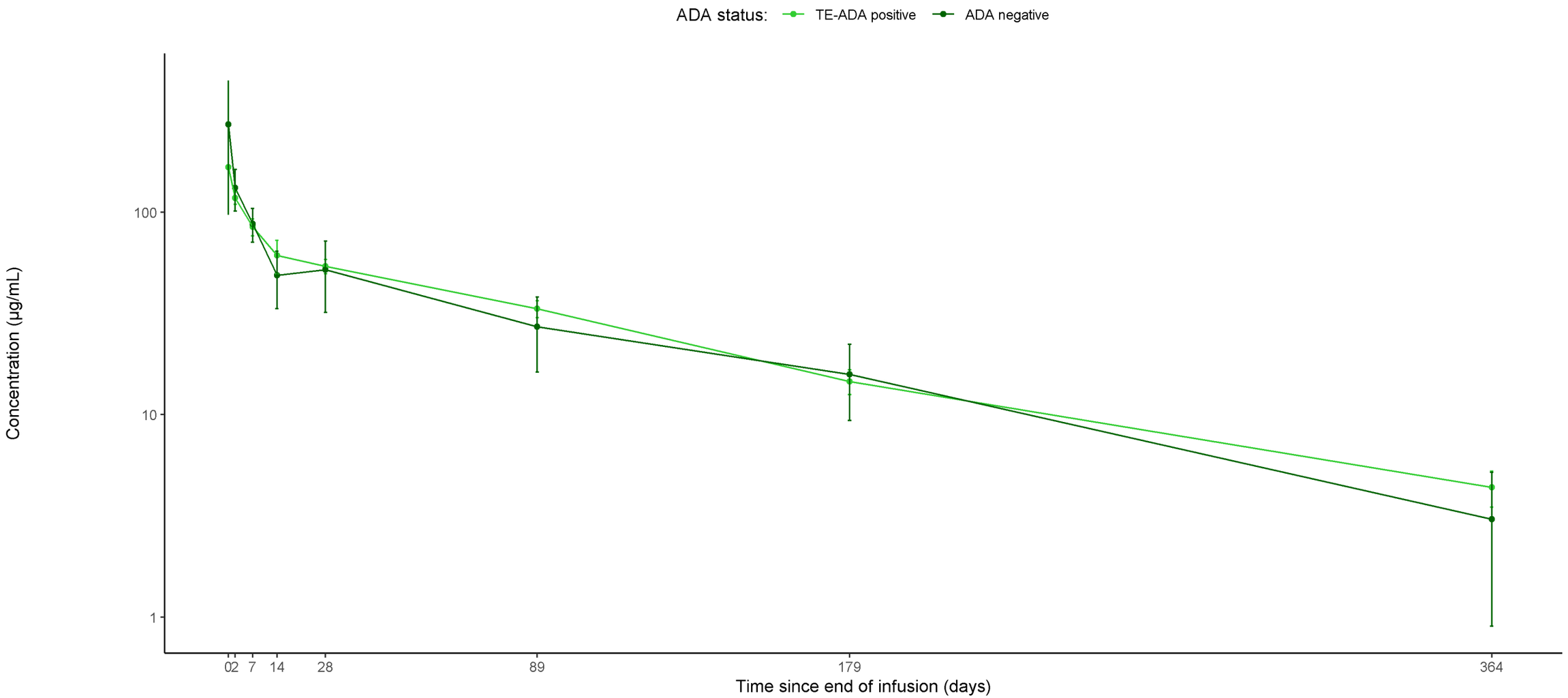
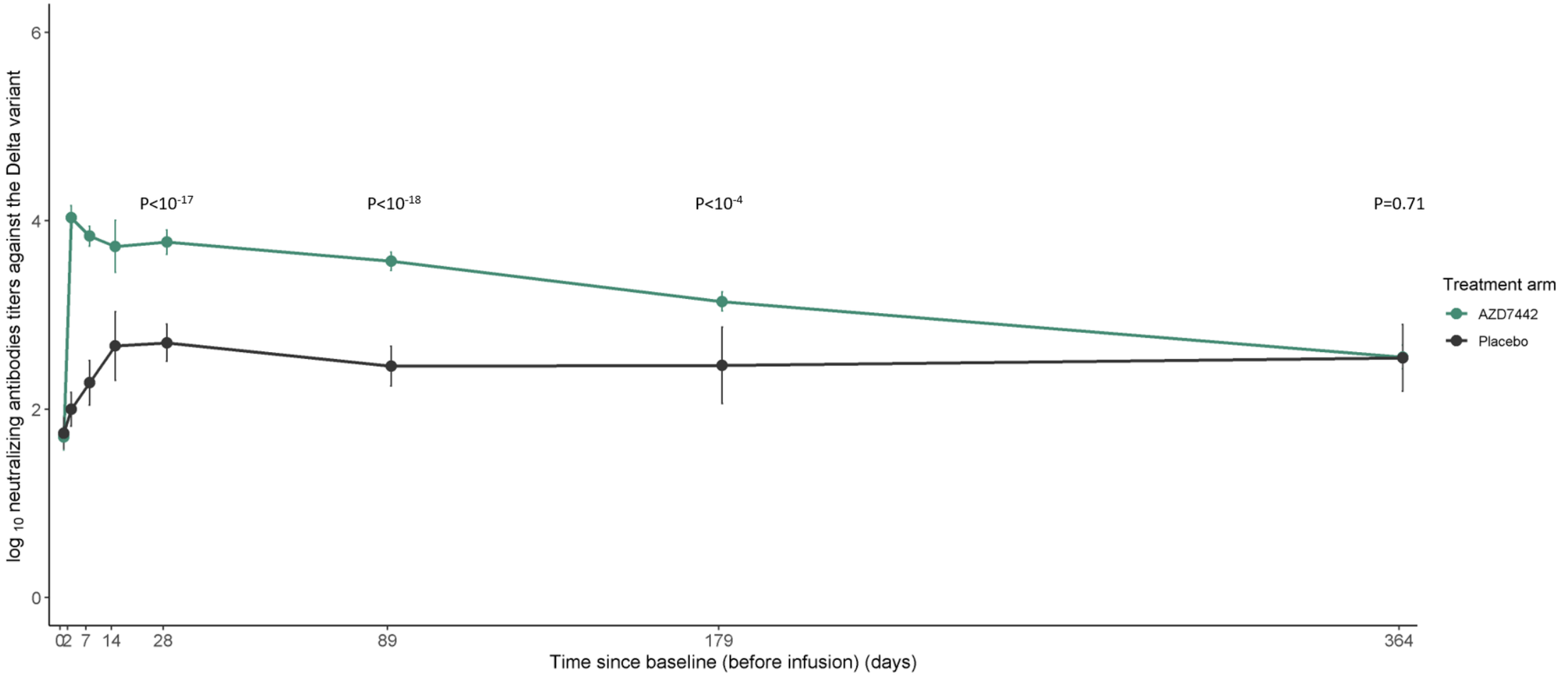


*consent form initially signed initially by the patient, but was later considered non-conform by the monitoring process
† non missing samples at baseline.
‡ non-missing baseline result and ≥ 1 non-missing result during follow-up



Number of available samples

TE-ADA positive	11	11	10	6	9	10	8	7
ADA negative	65	62	39	22	61	58	33	24



Number of available samples

AZD7442	118	105	65	29	77	74	43	34
Placebo	98	90	55	25	68	56	21	18

Number of undetectable measures

AZD7442	72	3	0	1	0	1	0	0
Placebo	58	34	14	3	8	9	3	2

Online Supplement to:

Efficacy, safety, pharmacokinetics, immunogenicity, and serum neutralizing activity of AZD7442 (tixagevimab-cilgavimab) in hospitalized COVID-19 patients: long-term results from the DisCoVeRy trial

Clément R. Massonnaud, Nathan Peiffer-Smadja, Pascal Poignard, et al. on behalf of the DisCoVeRy study group.

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Supplementary methods

Participants

Inclusion criteria:

- Adult ≥18 years of age at time of enrolment
- Hospitalized patients with any of the following criteria:
    - the presence of pulmonary rales/crackles on clinical exam OR
    - SpO2 ≤ 94% on room air OR
    - requirement of supplementary oxygen including high flow oxygen devices or non-invasive ventilation
- A time between onset of symptoms and randomization of less than 9 days (11 days from September 20th, 2021, protocol V15)
- A positive SARS-CoV-2 RT-PCR performed on a NP swab within the 5 days preceding randomization
- The result of a rapid antigen test performed on a NP swab within the 6 hours preceding randomization
- Contraceptive use by men or women
    - Male participants: Contraception for male participants is not required; however, to avoid the transfer of any fluids, all male participants must use a condom from Day 1 and agree to continue for 90 days following administration of IMP
    - Female participants: Women of child-bearing potential must agree to use contraception for 365 days following administration of IMP

Exclusion criteria:

- Refusal to participate expressed by patient or legally authorized representative if they are present
- Need for invasive mechanical ventilation and/or ECMO at the time of enrolment
- Spontaneous blood ALT/AST levels > 5 times the upper limit of normal
- Glomerular filtration rate (GFR) < 15 mL/min or requiring maintenance dialysis
- Pregnancy or breast-feeding
- Anticipated transfer to another hospital, which is not a study site within 72 hours following randomization
- Known history of allergy or reaction to any component of the study drug formulation
- Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of monoclonal or polyclonal antibodies.
- *Before September 20th, 2021:* any prior receipt of investigational or licensed vaccine
- Any prior receipt of investigational or licensed mAb indicated for the prevention of SARS-CoV-2 infection or COVID-19, and for those not vaccinated, expected receipt of vaccine in the 30 days following hospital discharge, according to current recommendation in each country.
- Any medical condition which, in the judgment of the investigator, could interfere with the interpretation of the trial results or that preludes to protocol adherence.

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Immunogenicity endpoints

Anti-drug antibody (ADA) titres were measured in serum samples on day 1 before infusion, and on days 15, 29, 90, 180, and 365. ADA positivity was defined as ADA titres ≥ 2 times the assay limit (i.e. ≥ 160 units for tixagevimab and ≥ 80 units for cilgavimab). ADA positivity to AZD7442 was defined as being ADA positive to either tixagevimab, cilgavimab, or both.

Treatment-induced ADA positivity was defined as being ADA negative at baseline and having at least one positive result post-baseline (i.e. ≥ 2 times the assay limit). Treatment-boosted ADA positivity was defined as having a baseline ADA titre that increased by ≥ 4 times following drug administration. Treatment-emergent ADA (TE-ADA) positivity, also known as ADA incidence, was defined as being either treatment-induced or treatment-boosted ADA positive. Non TE-ADA positivy was defined as having at least one ADA positive result at any time, but not meeting the criteria for TE-ADA positivity (also known as ADA prevalence). ADA negativity was defined as being ADA negative at all times.

Pharmacokinetics endpoints

Drug concentrations were measured in serum samples on day 1, both before and after the end of infusion, and on days 3, 8, 15, 29, 90, 180, and 365. Concentrations were measure separately for tixagevimab and cilgavimab, and AZD7442 concentration was defined as the sum of tixagevimab and cilgavimab concentrations.

Seroneutralization endpoints

Neutralizing antibody titres were measured in serum samples on days 1, 3, 8, 15, 29, 90, 180, and 365, and were reported as the 50% inhibitory dilution (ID50). The neutralizing activity against the Delta variant was measured in all participants. Additionally, neutralizing activity was assessed according to the variant of infection of each participant (against Omicron BA.1 for participants infected with Omicron BA.1, against the Omicron BA.2 for participants infected with Omicron BA.2 or BA.5, and against a Delta variant for participants infected with any pre-Omicron variant).

Sequencing methods

After extraction, SARS-CoV-2 sequencing was carried out using COVIDSeq-Test™ (Illumina, San Diego, USA) with Artic V3, V4 or V4.1 primers as they became available. Libraries were sequenced with 100 bp paired-end reads using the NovaSeq 6000 Sequencing system SP flow cell.

To interpret sequencing data, reads were processed using the in-house bioinformatic pipeline seqmet (available at https://github.com/genepii/seqmet). Briefly, trimming of paired reads was performed with cutadapt to remove sequencing adapters and low-quality ends. Alignment to the SARS-CoV-2 reference genome MN908947 was performed by minimap2. Duplicate reads tagged by picard were removed, remaining reads were realigned by abra2 to improve indel detection sensitivity and finally clipped with samtools ampliconclip to remove read ends containing primer sequences. Finally, variant calling was performed by freebayes.

Serology methods

The presence of anti-SARS-CoV-2 antibodies was evaluated on serum samples using the Atellica SARS-CoV-2 IgG assay (sCOVG, Siemens Healthineers, Erlangen, Germany), which detects and quantify IgG against RBD domain of the spike (S), and the Architect SARS-COV-2 IgG test (Abbott, Sligo, Ireland), which detects anti-nucleocapsid (N) IgG. Positivity was established according to the threshold value recommended by each manufacturer.

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As a quantitative assay, the index value (U/mL) obtain for the sCOVG assay correspond to 21.80 BAU/mL using the World Health Organization (WHO) 1st International 1.0 Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code: 20/136). This assay has a measuring interval of 0.50–150.00 Index (U/mL) but samples under 1.00 Index (U/mL) were reported as non-reactive reactive according to the manufacturers' instructions. In addition, any sample with a result above 150.00 index (U/mL) was automatically diluted 10 times to achieve a maximum limit of quantification of 1500 index (U/mL), i.e. 32700 BAU/mL.

Serum neutralization methods

Pseudovirus production and titration

Neutralization assays were performed using lentiviral pseudotypes harboring the SARS-CoV-2 spike and encoding luciferase. Briefly, adherent HEK293T cells were co-transfected with gag/pol and luciferase plasmids (kindly provided by Pierre Charneau, Institut Pasteur), alongside different SARS-CoV-2 spike plasmids (Delta, BA-1 or BA-2) from InvivoGen (plv-SpikeV8, V11 and V12, respectively). Pseudovirus-containing supernatants were harvested after 72 h, centrifuged and filtered through a 0.45 µm filter. Supernatants were then concentrated 50 times on Amicon Ultra (MWCO 100KDa), aliquoted and stored at −80°C. Before use, pseudovirus preparations were tittered using HeLa ACE-2 cells to determine the appropriate dilution necessary to obtain about 150,000 relative light units (RLU) per well in 96-w white plates (Corning #3885).

Neutralization assay

Sequential 1/3 dilutions of serum, starting at a 1/10, and Evusheld, starting at varying concentrations depending on the pseudovirus type (Delta: 0.9µg/ml, BA-1: 60µg/ml, BA-2: 2 µg/ml), were incubated with pseudoviruses for 1 h at 37°C in 96-well white plates, before addition of HeLa ACE2 cells (8000 cells per well, kindly provided by David Nemazee, Scripps Research). Subsequently, plates were incubated for 24 h at 37°C, while being protected from evaporation. After this incubation period, 40µL of DMEM (Gibco 21969035) supplemented with 10% FBS (VWR 97068-086) were added to each well. Following another 24 h of incubation, the medium in each well was aspirated and replaced by 45 µL of 1x cell lysis buffer (OZ Bioscience # LUC1000) for a 60-min incubation under agitation. Thirty µL of luciferin substrate were then added and relative light units (RLU) were measured immediately using a luminometer. The IC50 values were calculated using GraphPad Prism (Version 10).

Statistical methods

Handling of missing data

Missing data for the ordinal scale was handled as follows : if the last scale value available before the missing data for a patient is 7 (death), or if a death date is available, the value for the ordinal scale will be imputed to 7 and carried forward for all subsequent endpoints. For non-hospitalized patients, if the last available value is 1 (not hospitalized, no limitations on activities) or 2 (hospitalized, with limitations on activities), it will be carried forward, otherwise, it will be imputed to 2. For hospitalized patients, a value of 3 (hospitalized, not requiring supplemental oxygen), 4 (hospitalized, requiring supplemental oxygen), 5 (hospitalized on non-invasive ventilation or high flow oxygen devices), or 6 (hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation) will be imputed based on the available clinical data on the day of the missing value, and carried forward until the next non-missing value, or the discharge date, or the date of death.

Missing data for the NEWS-2 score were imputed to the mean if they were missing at baseline.

If a patient was discharged and no further hospitalization data is available, then the patient will be considered as not being re-hospitalised afterwards. If the ordinal scale value on a given day is "1. Not hospitalized, no limitations on activities" or "2. Not hospitalized, limitation on activities", but the value for the date of discharge is missing, it will be imputed to the day preceding the date on which the ordinal scale value was available.

If the ordinal scale value on a given day is "7. Death", but the date of death is missing, it will be imputed to the first date associated with the ordinal scale value "7. Death".

Missing data for variant of infection was handled as follows: if sequencing data for variant was missing at baseline, it was imputed using available sequencing data for variant at day 3 or day 8. If no sequencing data was available, the variant of infection was imputed to be the variant that was dominant in France at the time of the patient's symptoms onset, according to epidemiological surveys.[1] We identified three periods in which a single variant was dominant (estimated to represent more than 95% of infections): (a) pre-Omicron variant before December 9, 2021; (b) Omicron BA.1 from January 6, 2022 to January 24, 2022; (c) Omicron BA.2/5 after March 28, 2022. If the patient's date of symptom onset fell into a period of transition of circulating variants (from December 9, 2021 to January 6, 2022, or from January 24, 2022 to March 28, 2022), the variant of infection remained "unknown".

Missing viral loads were not imputed. Undetectable viral load values (i.e. values < 1 $\log_{10}$ copies/10 000 cells) were imputed 0.7 $\log_{10}$ copies/10 000 cells.

Missing neutralizing antibody titres were not imputed. For this analysis, the LOD was defined at a value of 30. Values below the LOD (either undetectable or < 30) were imputed to 15 in some analyses.

Statistical analyses

ADA analyses were conducted on the global mITT population, in participants with non-missing baseline tixagevimab and cilgavimab ADA results, and having at least one non-missing post-baseline tixagevimab and cilgavimab ADA result. Pharmacokinetic analyses were performed on participants from the global mITT population, randomized to the AZD7442 group. Seroneutralization analyses were performed on the global mITT population.

The number and proportion of participants TE-ADA positive, non-TE-ADA positive, and ADA-negative were described separately for tixagevimab, cilgavimab, and AZD7442, overall and according to the treatment group. For TE-ADA positive participants, the median and range of the maximum titres were also reported. AZD7442 serum concentrations were described at each time by the mean concentrations and their estimated 95% confidence interval (CI), overall and stratified by the ADA positivity status. A post-hoc comparison of the proportions of TE-ADA positive participants in the AZD7442 group compared to placebo was performed using the Cochran-Mantel-Haenszel test, stratified according to vaccination status (initiated yes or no).

The neutralizing antibody titres (ID50) were log-transformed and described at each time by their mean and 95% CI, according to the treatment group. The log10 ID50 on days 29, 90, 180, and 365 were compared between the two treatment groups using ANCOVA models and results were reported as least-square mean differences (LSMD), adjusted for the vaccination status (initiated yes or no) and the variant of infection (pre-Omicron, Omicron BA.1, Omicron BA.2/5).

A post-hoc analysis of neutralizing antibody levels against the Delta variant was performed using a linear mixed-effects model (LME) with a random intercept for each participant to account for repeated measurements over time from day 3 to day 365. The fixed effects included time, treatment group (AZD7442 vs. control), vaccination status (yes/no), and variant of infection (pre-Omicron, Omicron BA.1, Omicron BA.2), as well as their interactions with time to assess differential temporal trajectories. Model estimates are reported as regression coefficients with corresponding 95% confidence intervals and p-values.

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Trial safety and monitoring

There was no pre-planned interim analysis for efficacy nor futility, and none was performed. Data on adverse events and serious adverse events were reviewed monthly by the safety department. An independent data safety and monitoring board (DSMB) externally reviewed the trial data at regular intervals regarding treatment efficacy, safety, and futility. The DSMB gathered as planned after the inclusion of the first 100 patients, on April 20th, 2022, and recommended the continuation of the study.

The protocol specified a list of disease-related events (DREs) which refer to complications that are common in hospitalized patients with COVID-19 and can be serious. DREs were systematically collected in the eCRF but did not require immediate reporting to the sponsor as SAEs, unless assessed as possibly related to the blinded IMP by the investigator.

This list included the following DREs: acute kidney injury/acute renal failure, grade 3 and above transaminase increased, pancreatitis, bacteraemia, bacterial pneumonia, cardiac arrhythmia, cardiac ischemia, cardiac arrest, endocarditis, myocarditis, pericarditis, congestive heart failure, acute respiratory distress syndrome, pneumothorax, pleural effusion, meningitis, encephalitis, stroke, coma, confusion, gastrointestinal hemorrhage, pulmonary thrombosis, arterial or deep vein thromboembolic events.

In the protocol, the adverse events of special interest (AESI) were defined as anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, or grade 3 and 4 injection site reactions or infusion-related events. All AESIs required immediate notification to the sponsor.

References

1. Coronavirus : chiffres clés et évolution de la COVID-19 en France et dans le Monde [Internet]. [cited 2023 Nov 3]. Available from: https://www.santepubliquefrance.fr/dossiers/coronavirus-covid-19/coronavirus-chiffres-cles-et-evolution-de-la-covid-19-en-france-et-dans-le-monde

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Supplementary results

Supplementary table S1. Follow-up at each time

	Global (N=226)		
	Overall (N=226)	**AZD7442** (N=123)	**Placebo** (N=103)
Day 1			
In hospital	226 (100%)	123 (100%)	103 (100%)
Serum samples	221 (97.8%)	121 (98.4%)	100 (97.1%)
Day 3			
In hospital	220 (97.3%)	121 (98.4%)	99 (96.1%)
Serum samples	203 (89.8%)	111 (90.2%)	92 (89.3%)
Day 8			
In hospital	119 (52.7%)	66 (53.7%)	53 (51.5%)
Serum samples	106 (46.9%)	57 (46.3%)	49 (47.6%)
Day 15			
In hospital	44 (19.5%)	25 (20.3%)	19 (18.4%)
Phone call	158 (69.9%)	87 (70.7%)	71 (68.9%)
Serum samples	40 (17.7%)	23 (18.7%)	17 (16.5%)
Day 29			
In hospital	20 (8.8%)	14 (11.4%)	6 (5.8%)
Phone call	167 (73.9%)	91 (74.0%)	76 (73.8%)
Serum samples	149 (65.9%)	79 (64.2%)	70 (68.0%)
Day 90			
Outpatient visit	177 (78.3%)	99 (80.5%)	78 (75.7%)
Serum samples	135 (59.7%)	77 (62.6%)	58 (56.3%)
Day 180			
Outpatient visit	168 (74.3%)	97 (78.9%)	71 (68.9%)
Serum samples	67 (29.6%)	45 (36.6%)	22 (21.4%)
Day 365			
Outpatient visit	156 (69.0%)	89 (72.4%)	67 (65.0%)
Serum sample	54 (23.9%)	36 (29.3%)	18 (17.5%)
Day 456			
Phone call	151 (66.8%)	88 (71.5%)	63 (61.2%)

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Supplementary table S2. Clinical endpoints in the antigen positive and global modified intention to treat populations, overall and according to the treatment group.

	Antigen positive (N=173)				Global (N=226)			
	Overall (N=173)	AZD7442 (N=91)	Placebo (N=82)	AZD7442 vs. Placebo Effect measure (95%CI)	Overall (N=226)	AZD7442 (N=123)	Placebo (N=103)	AZD7442 vs. Placebo Effect measure (95%CI)
7-point ordinal scale at day 180, n (%)								
1. Not hospitalized, no limitations on activities	96 (55.5%)	46 (50.5%)	50 (61.0%)		129 (57.1%)	66 (53.7%)	63 (61.2%)	
2. Not hospitalized, limitation on activities	43 (24.9%)	28 (30.8%)	15 (18.3%)		58 (25.7%)	38 (30.9%)	20 (19.4%)	
3. Hospitalized, not requiring supplemental oxygen	6 (3.5%)	4 (4.4%)	2 (2.4%)		6 (2.7%)	4 (3.3%)	2 (1.9%)	
4. Hospitalized, requiring supplemental oxygen	1 (0.6%)	1 (1.1%)	0 (0.0%)	OR=0.78 (0.43 to 1.40) [P=0.40]	1 (0.4%)	1 (0.8%)	0 (0.0%)	OR=0.88 (0.52 to 1.49) [P=0.64]
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices					1 (0.4%)	1 (0.8%)	0 (0.0%)	
7. Death	27 (15.6%)	12 (13.2%)	15 (18.3%)		31 (13.7%)	13 (10.6%)	18 (17.5%)	
7-point ordinal scale at day 365, n (%)								
1. Not hospitalized, no limitations on activities	100 (57.8%)	50 (54.9%)	50 (61.0%)		135 (59.7%)	72 (58.5%)	63 (61.2%)	
2. Not hospitalized, limitation on activities	35 (20.2%)	21 (23.1%)	14 (17.1%)		47 (20.8%)	29 (23.6%)	18 (17.5%)	
3. Hospitalized, not requiring supplemental oxygen	5 (2.9%)	4 (4.4%)	1 (1.2%)	OR=0.89 (0.49 to 1.61) [P=0.70]	6 (2.7%)	4 (3.3%)	2 (1.9%)	OR=1.05 (0.62 to 1.78) [P=0.85]
4. Hospitalized, requiring supplemental oxygen	1 (0.6%)	1 (1.1%)	0 (0.0%)		1 (0.4%)	1 (0.8%)	0 (0.0%)	
7. Death	32 (18.5%)	15 (16.5%)	17 (20.7%)		37 (16.4%)	17 (13.8%)	20 (19.4%)	
In hospital mortality rate, n (%)	21 (12.1%)	9 (9.9%)	12 (14.6%)	OR=0.64 (0.25 to 1.61) [P=0.34]	23 (10.2%)	9 (7.3%)	14 (13.6%)	OR=0.49 (0.20 to 1.19) [P=0.11]
Mortality rate at Day 180, n (%)	27 (15.6%)	12 (13.2%)	15 (18.3%)	OR=0.67 (0.29 to 1.56) [P=0.35]	31 (13.7%)	13 (10.6%)	18 (17.5%)	OR=0.53 (0.24 to 1.17) [P=0.12]
Mortality rate at Day 365, n (%)	32 (18.5%)	15 (16.5%)	17 (20.7%)	OR=0.74 (0.33 to 1.65) [P=0.46]	37 (16.4%)	17 (13.8%)	20 (19.4%)	OR=0.63 (0.30 to 1.32) [P=0.22]
Mortality rate at day 456, n (%)	33 (19.1%)	16 (17.6%)	17 (20.7%)	OR=0.80 (0.36 to 1.78) [P=0.59]	39 (17.3%)	19 (15.4%)	20 (19.4%)	OR=0.72 (0.35 to 1.50) [P=0.39]

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	Antigen positive (N=173)				Global (N=226)			
	Overall (N=173)	AZD7442 (N=91)	Placebo (N=82)	AZD7442 vs. Placebo Effect measure (95%CI)	Overall (N=226)	AZD7442 (N=123)	Placebo (N=103)	AZD7442 vs. Placebo Effect measure (95%CI)
Occurrence of new hospitalization between discharge from index hospital and Days 180, n (%)	19 (11.0%)	12 (13.2%)	7 (8.5%)	OR=1.63 (0.61 to 4.38) [P=0.33]	33 (14.6%)	22 (17.9%)	11 (10.7%)	OR=1.83 (0.83 to 4.03) [P=0.13]
Occurrence of new hospitalization between discharge from index hospital and Days 365, n (%)	29 (16.8%)	19 (20.9%)	10 (12.2%)	OR=1.92 (0.83 to 4.43) [P=0.13]	44 (19.5%)	30 (24.4%)	14 (13.6%)	OR=2.08 (1.02 to 4.22) [P=0.04]
Occurrence of new hospitalization between discharge from index hospital and Days 456, n (%)	33 (19.1%)	21 (23.1%)	12 (14.6%)	OR=1.78 (0.80 to 3.94) [P=0.15]	49 (21.7%)	33 (26.8%)	16 (15.5%)	OR=2.04 (1.03 to 4.05) [P=0.04]
Confirmed re-infection with SARS-CoV-2 between discharge from index hospital and Days 90, n (%)	4 (3.0%)	2 (2.8%)	2 (3.1%)	OR=0.88 (0.12 to 6.42) [P=0.90]	5 (2.7%)	3 (2.9%)	2 (2.5%)	OR=1.12 (0.18 to 6.92) [P=0.90]
Confirmed re-infection with SARS-CoV-2 between discharge from index hospital and Days 180, n (%)	6 (4.6%)	3 (4.3%)	3 (5.0%)	OR=0.84 (0.16 to 4.36) [P=0.84]	7 (4.0%)	4 (4.0%)	3 (4.0%)	OR=0.95 (0.20 to 4.44) [P=0.95]
Confirmed re-infection with SARS-CoV-2 between discharge from index hospital and Days 365, n (%)	17 (14.3%)	11 (17.5%)	6 (10.7%)	OR=1.75 (0.60 to 5.08) [P=0.31]	22 (13.7%)	14 (15.2%)	8 (11.6%)	OR=1.37 (0.54 to 3.47) [P=0.51]
Confirmed re-infection with SARS-CoV-2 between discharge from index hospital and Days 456, n (%)	22 (19.5%)	12 (19.7%)	10 (19.2%)	OR=1.03 (0.40 to 2.62) [P=0.95]	29 (19.1%)	17 (19.3%)	12 (18.8%)	OR=1.04 (0.46 to 2.35) [P=0.93]

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Supplementary table S3. Missing data for the clinical endpoints

	Global (N=226)		
	Overall (N=226)	**AZD7442 (N=123)**	**Placebo (N=103)**
7-point ordinal scale on day 15	24/226 (10.6%)	11/123 (8.9%)	13/103 (12.6%)
7-point ordinal scale on day 180	58/226 (25.7%)	26/123 (21.1%)	32/103 (31.1%)
7-point ordinal scale on day 365	70/226 (31.0%)	34/123 (27.6%)	36/103 (35.0%)
Vital status on day 456	75/226 (33.2%)	35/123 (28.5%)	40/103 (38.8%)
Occurrence of new hospitalization between day 91 and day 180	63/226 (27.9%)	31/123 (25.2%)	32/103 (31.1%)
Occurrence of new hospitalization between day 181 and day 365	72/226 (31.9%)	35/123 (28.5%)	37/103 (35.9%)
Occurrence of new hospitalization between day 366 and day 456	75/226 (33.2%)	35/123 (28.5%)	40/103 (38.8%)
Confirmed re-infection with SARS-CoV-2 between discharge from index hospital and day 90	49/226 (21.7%)	24/123 (19.5%)	25/103 (24.3%)
Confirmed re-infection with SARS-CoV-2 between day 91 and day 180	58/226 (25.7%)	26/123 (21.1%)	32/103 (31.1%)
Confirmed re-infection with SARS-CoV-2 between day 181 and day 365	70/226 (31.0%)	34/123 (27.6%)	36/103 (35.0%)
Confirmed re-infection with SARS-CoV-2 between day 366 and day 456	75/226 (33.2%)	35/123 (28.5%)	40/103 (38.8%)

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Supplementary table S4. Antidrug antibody positivity to tixagevimab, cilgavimab, or AZD7442 through day 365.

	ADA-Tixagevimab			ADA- Cilgavimab			ADA-AZD7442		
	Overall (N=156)	AZD7442 (N=87)	Placebo (N=69)	Overall (N=156)	AZD7442 (N=87)	Placebo (N=69)	Overall (N=156)	AZD7442 (N=87)	Placebo (N=69)
ADA positive									
- at baseline, n/N (%)	4/156 (2.6%)	2/87 (2.3%)	2/69 (2.9%)	2/155 (1.3%)	1/87 (1.1%)	1/68 (1.5%)	5/156 (3.2%)	2/87 (2.3%)	3/69 (4.3%)
- at Day 15, n/N (%)	9/52 (17.3%)	6/29 (20.7%)	3/23 (13.0%)	7/52 (13.5%)	5/29 (17.2%)	2/23 (8.7%)	9/52 (17.3%)	6/29 (20.7%)	3/23 (13.0%)
- at Day 29, n/N (%)	6/134 (4.5%)	1/72 (1.4%)	5/62 (8.1%)	4/132 (3.0%)	3/71 (4.2%)	1/61 (1.6%)	9/132 (6.8%)	4/71 (5.6%)	5/61 (8.2%)
- at Day 90, n/N (%)	3/122 (2.5%)	2/70 (2.9%)	1/52 (1.9%)	5/117 (4.3%)	4/65 (6.2%)	1/52 (1.9%)	6/117 (5.1%)	4/65 (6.2%)	2/52 (3.8%)
- at Day 180, n/N (%)	2/58 (3.4%)	1/41 (2.4%)	1/17 (5.9%)	2/55 (3.6%)	2/39 (5.1%)	0/16 (0.0%)	3/55 (5.5%)	2/39 (5.1%)	1/16 (6.3%)
- at Day 365, n/N (%)	0/47 (0.0%)	0/31 (0.0%)	0/16 (0.0%)	2/45 (4.4%)	1/30 (3.3%)	1/15 (6.7%)	2/45 (4.4%)	1/30 (3.3%)	1/15 (6.7%)
TE-ADA positive through 365 days, n/N (%)	13/156 (8.3%)	9/87 (10.3%)	4/69 (5.8%)	13/156 (8.3%)	10/87 (11.5%)	3/69 (4.3%)	17/156 (10.9%)	12/87 (13.8%)	5/69 (7.2%)
Non TE-ADA positive, n/N (%)	4/156 (2.6%)	2/87 (2.3%)	2/69 (2.9%)	2/156 (1.3%)	1/87 (1.1%)	1/69 (1.4%)	4/156 (2.6%)	1/87 (1.1%)	3/69 (4.3%)
ADA negative through 365 days, n/N (%)	139/156 (89.1%)	76/87 (87.4%)	63/69 (91.3%)	141/156 (90.4%)	76/87 (87.4%)	65/69 (94.2%)	135/156 (86.5%)	74/87 (85.1%)	61/69 (88.4%)

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Supplementary table S5. Maximum antidrug antibodies titres through day 365 in TE-ADA positive participants, for tixagevimab, cilgavimab, and for AZD7442 in each treatment group.

	ADA-Tixagevimab			ADA-Cilgavimab			ADA-AZD7442		
	Overall (N=156)	AZD7442 (N=87)	Placebo (N=69)	Overall (N=156)	AZD7442 (N=87)	Placebo (N=69)	Overall (N=156)	AZD7442 (N=87)	Placebo (N=69)
n	13	9	4	13	10	3	34	24	10
Missing data	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (20.6%)	4 (16.7%)	3 (30.0%)
Available data	13	9	4	13	10	3	27	20	7
Minimum / Maximum	160.0 / 1280.0	160.0 / 1280.0	160.0 / 1280.0	80.0 / 640.0	80.0 / 640.0	80.0 / 320.0	80.0 / 1280.0	80.0 / 1280.0	80.0 / 1280.0
Median [IQR]	320.0 [160.0-640.0]	320.0 [160.0-320.0]	800.0 [240.0-1280.0]	320.0 [160.0-640.0]	240.0 [160.0-640.0]	320.0 [80.0-320.0]	320.0 [160.0-640.0]	320.0 [160.0-640.0]	320.0 [160.0-1280.0]
Mean (SD)	504.6 (461.2)	391.1 (367.6)	760.0 (604.0)	326.2 (234.3)	352.0 (256.3)	240.0 (138.6)	411.9 (363.0)	368.0 (297.5)	537.1 (515.8)

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Supplementary table S6. AZD7442 serum concentration at each sampling time, overall and by anti-drug antibodies (ADA) positivity status

	Overall (N=116)	ADA negative (N=74)	TE-ADA positive (N=12)
Day 1, before infusion			
Available data	111	69	12
Missing data	5 (4.3)	5 (6.8)	0 (0)
(Min - Max)	(0.3 - 0.3)	(0.3 - 0.3)	(0.3 - 0.3)
Median [IQR]	0.3 [0.3 ; 0.3]	0.3 [0.3 ; 0.3]	0.3 [0.3 ; 0.3]
Mean (SD)	0.3 (0)	0.3 (0)	0.3 (0)
Day 1, end of infusion			
Available data	105	65	11
Missing data	11 (9.5)	9 (12.2)	1 (8.3)
(Min - Max)	(76.3 - 1026.36)	(76.3 - 350.57)	(98.75 - 1026.36)
Median [IQR]	166.15 [144.3 ; 202.21]	161.97 [142.06 ; 185.99]	193.7 [162.44 ; 252.29]
Mean (SD)	183.17 (99.16)	166.6 (47.07)	271.3 (259.35)
Day 3			
Available data	96	62	11
Missing data	20 (17.2)	12 (16.2)	1 (8.3)
(Min - Max)	(59.64 - 234.55)	(59.64 - 225.08)	(76.86 - 223.88)
Median [IQR]	115.62 [99.15 ; 144.49]	112.8 [97.5 ; 132.65]	123.72 [102.41 ; 142.19]
Mean (SD)	124.39 (39.22)	117.46 (33.19)	131.74 (45.29)
Day 8			
Available data	62	39	10
Missing data	54 (46.6)	35 (47.3)	2 (16.7)
(Min - Max)	(44.79 - 170.34)	(44.79 - 170.34)	(51.23 - 127.63)
Median [IQR]	84.64 [69.42 ; 99.53]	80.12 [69.47 ; 91.87]	85.52 [79.68 ; 100.03]
Mean (SD)	86.66 (25.64)	84.37 (24.9)	87.47 (23.15)
Day 15			
Available data	30	22	6
Missing data	86 (74.1)	52 (70.3)	6 (50)
(Min - Max)	(18.63 - 140.41)	(18.63 - 140.41)	(26.34 - 67.92)
Median [IQR]	55.33 [43.4 ; 67.29]	57.25 [50.52 ; 68.31]	49.1 [41.89 ; 57.49]
Mean (SD)	58.45 (24.64)	61.07 (26.04)	48.71 (14.66)

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Day 29				
	Available data	76	61	9
	Missing data	40 (34.5)	13 (17.6)	3 (25)
	(Min - Max)	(7.74 - 105.07)	(11.41 - 93.12)	(7.74 - 88.19)
	Median [IQR]	55.63 [43.85 ; 64.64]	55.27 [44.22 ; 64.44]	60.31 [30.36 ; 64.37]
	Mean (SD)	54.33 (18.24)	53.94 (16.6)	51.94 (25.92)
Day 90				
	Available data	73	58	10
	Missing data	43 (37.1)	16 (21.6)	2 (16.7)
	(Min - Max)	(3.92 - 71.84)	(7.52 - 66.26)	(3.92 - 56.47)
	Median [IQR]	31.69 [23.94 ; 39.71]	31.74 [25.61 ; 39.27]	26.58 [17.53 ; 35.26]
	Mean (SD)	33.22 (13.5)	33.33 (12.21)	27.12 (15.23)
Day 180				
	Available data	44	33	8
	Missing data	72 (62.1)	41 (55.4)	4 (33.3)
	(Min - Max)	(2.54 - 31.28)	(2.54 - 24.29)	(7.05 - 31.28)
	Median [IQR]	14.51 [10.87 ; 19.37]	14.99 [10.99 ; 19.31]	14.01 [12.15 ; 17.56]
	Mean (SD)	14.9 (6.39)	14.59 (5.81)	15.8 (7.69)
Day 365				
	Available data	35	24	7
	Missing data	81 (69.8)	50 (67.6)	5 (41.7)
	(Min - Max)	(0.65 - 9.64)	(1.03 - 9.64)	(0.65 - 7.64)
	Median [IQR]	3.6 [2.37 ; 5.27]	4.25 [3.02 ; 5.12]	2.23 [1.95 ; 3.46]
	Mean (SD)	4.18 (2.37)	4.37 (2.09)	3.05 (2.32)

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Supplementary table S7. Neutralizing activity against the Delta variant. Proportion of patients with an undetectable neutralizing antibodies titres, log_{10} neutralizing antibodies titres (ID_{50}), and change from baseline of log_{10} neutralizing antibodies titres at each sampling time, overall and according to the treatment group.

For all analyses, we consider the ID_{50} titres of neutralizing antibodies targeted at the variant corresponding to the variant of infection at baseline of the patient. Reported OR and LSMD were adjusted by vaccination status and by variant of infection at baseline.

CI: confidence interval; LSMD: least squares mean difference.

	Global (N=226)			
	Overall (N=226)	AZD7442 (N=123)	Placebo (N=103)	AZD7442 vs. Placebo Effect measure (95%CI)
Undetectable neutralizing antibodies, n/N (%)				
- Baseline	130/216 (60.2%)	72/118 (61.0%)	58/98 (59.2%)	
- Day 3	37/195 (19.0%)	3/105 (2.9%)	34/90 (37.8%)	
- Day 8	14/120 (11.7%)	0/65 (0.0%)	14/55 (25.5%)	
- Day 15	4/54 (7.4%)	1/29 (3.4%)	3/25 (12.0%)	
- Day 29	8/145 (5.5%)	0/77 (0.0%)	8/68 (11.8%)	
- Day 90	10/131 (7.6%)	1/75 (1.3%)	9/56 (16.1%)	
- Day 180	3/64 (4.7%)	0/43 (0.0%)	3/21 (14.3%)	
- Day 365	2/52 (3.8%)	0/34 (0.0%)	2/18 (11.1%)	
Log10 neutralizing antibodies titres, median (IQR)				
- Baseline	1.2 [1.2-2.3]	1.2 [1.2-2.3]	1.2 [1.2-2.3]	
- Day 3	3.6 [1.7-4.1]	4.1 [3.9-4.4]	1.7 [1.2-2.6]	LSMD=2.05 (1.84 to 2.27) [$p<10^{-44}$]
- Day 8	3.4 [2.4-4.0]	3.9 [3.5-4.1]	2.4 [1.2-2.9]	LSMD=1.55 (1.31 to 1.79) [$p<10^{-22}$]
- Day 15	3.6 [2.5-4.0]	4.0 [3.6-4.1]	2.8 [1.9-3.4]	LSMD=1.05 (0.54 to 1.56) [p<0.001]
- Day 29	3.7 [2.6-3.9]	3.9 [3.7-4.0]	2.7 [2.2-3.4]	LSMD=1.10 (0.88 to 1.31) [$p<10^{-17}$]
- Day 90	3.4 [2.6-3.7]	3.7 [3.4-3.8]	2.4 [1.9-3.1]	LSMD=1.13 (0.92 to 1.33) [$p<10^{-18}$]
- Day 180	3.0 [2.7-3.3]	3.1 [2.9-3.3]	2.2 [2.0-3.1]	LSMD=0.66 (0.36 to 0.96) [$p<10^{-4}$]
- Day 365	2.6 [2.2-2.8]	2.6 [2.2-2.8]	2.5 [2.1-3.2]	LSMD=0.06 (-0.25 to 0.37) [p=0.71]

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	Global (N=226)			
	Overall (N=226)	**AZD7442 (N=123)**	**Placebo (N=103)**	**AZD7442 vs. Placebo Effect measure (95%CI)**
Change from baseline of log10 neutralizing antibodies, median (IQR)				
- Day 3	0.9 [0.1-2.7]	2.7 [1.7-3.0]	0.1 [0.0-0.5]	
- Day 8	1.6 [0.5-2.5]	2.4 [1.7-2.8]	0.5 [0.0-1.2]	
- Day 15	1.4 [0.7-2.5]	2.4 [1.4-2.8]	1.0 [0.1-1.6]	
- Day 29	1.7 [0.9-2.5]	2.5 [1.6-2.7]	1.1 [0.3-1.7]	
- Day 90	1.3 [0.6-2.2]	2.1 [1.2-2.5]	0.7 [0.0-1.3]	
- Day 180	1.4 [0.4-1.9]	1.5 [0.8-2.0]	0.4 [0.0-1.4]	
- Day 365	1.0 [0.0-1.5]	1.0 [0.1-1.5]	1.2 [-0.2-1.5]	

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Supplementary table S8. Neutralizing activity against the each participant's variant of infection. Proportion of patients with an undetectable neutralizing antibodies titres, log_{10} neutralizing antibodies titres (ID_{50}), and change from baseline of log_{10} neutralizing antibodies titres at each sampling time, overall and according to the treatment group.

For all analyses, we consider the ID_{50} titres of neutralizing antibodies targeted at the variant corresponding to the variant of infection at baseline of the patient. Reported OR and LSMD were adjusted by vaccination status and by variant of infection at baseline.

CI: confidence interval; LSMD: least squares mean difference.

	Global (N=208)			
	Overall (N=208)	AZD7442 (N=113)	Placebo (N=95)	AZD7442 vs. Placebo Effect measure (95%CI)
Undetectable neutralizing antibodies, n/N (%)				
Baseline	105/198 (53.0%)	56/108 (51.9%)	49/90 (54.4%)	
Day 3	26/179 (14.5%)	1/97 (1.0%)	25/82 (30.5%)	
Day 8	7/112 (6.3%)	0/60 (0.0%)	7/52 (13.5%)	
Day 15	3/51 (5.9%)	1/26 (3.8%)	2/25 (8.0%)	
Day 29	5/133 (3.8%)	0/71 (0.0%)	5/62 (8.1%)	
Day 90	8/120 (6.7%)	2/69 (2.9%)	6/51 (11.8%)	
Day 180	4/59 (6.8%)	2/40 (5.0%)	2/19 (10.5%)	
Day 365	3/48 (6.3%)	1/31 (3.2%)	2/17 (11.8%)	
Log10 neutralizing antibodies titres, median (IQR)				
Baseline	1.2 [1.2-2.4]	1.2 [1.2-2.3]	1.2 [1.2-2.5]	
Day 3	3.2 [2.1-3.9]	3.8 [3.3-4.1]	2.1 [1.2-3.0]	LSMD=1.44 (1.20 to 1.68) [$p < 10^{-23}$]
Day 8	3.3 [2.6-3.8]	3.5 [3.3-4.0]	2.7 [2.0-3.4]	LSMD=0.91 (0.64 to 1.18) [$p < 10^{-8}$]
Day 15	3.5 [2.7-3.9]	3.7 [3.1-4.1]	3.0 [2.3-3.5]	LSMD=0.65 (0.15 to 1.15) [p =0.014]
Day 29	3.6 [2.8-3.9]	3.8 [3.3-4.1]	2.9 [2.5-3.7]	LSMD=0.64 (0.41 to 0.88) [$p<10^{-6}$]
Day 90	3.2 [2.6-3.7]	3.6 [3.1-3.8]	2.7 [2.0-3.5]	LSMD=0.71 (0.46 to 0.96) [$p < 10^{-6}$]
Day 180	3.0 [2.3-3.3]	3.0 [2.7-3.3]	2.3 [1.9-3.2]	LSMD=0.50 (0.14 to 0.85) [p < 0.01]
Day 365	2.6 [2.1-3.1]	2.6 [2.2-3.0]	2.5 [2.1-3.2]	LSMD=0.08 (-0.26 to 0.41) [p =0.65]

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	Global (N=208)			
	Overall (N=208)	**AZD7442 (N=113)**	**Placebo (N=95)**	**AZD7442 vs. Placebo Effect measure (95%CI)**
Change from baseline of log10 neutralizing antibodies, median (IQR)				
Day 3	0.8 [0.3-2.1]	2.0 [0.9-2.7]	0.3 [0.0-0.6]	
Day 8	1.3 [0.7-2.2]	1.9 [1.1-2.4]	0.8 [0.2-1.4]	
Day 15	1.4 [0.7-2.4]	2.0 [1.0-2.8]	1.2 [0.3-2.1]	
Day 29	1.5 [0.8-2.3]	1.9 [1.0-2.6]	1.2 [0.6-1.7]	
Day 90	1.2 [0.5-1.9]	1.6 [0.6-2.3]	0.8 [0.0-1.4]	
Day 180	1.1 [0.3-1.7]	1.4 [0.5-1.7]	0.4 [-0.1-1.5]	
Day 365	0.9 [0.0-1.4]	0.8 [0.0-1.4]	1.0 [0.0-1.4]	

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Supplementary table S9: Linear mixed-effects model assessing the temporal evolution of neutralizing antibody levels against the Delta variant, from day 3 to day 365, according to treatment group (AZD7442/placebo), vaccination status (vaccinated/unvaccinated), and variant of infection (pre-Omicron/Omicron BA-1/Omicron BA-2).

	Estimate	95% confidence interval	p-value
Intercept	2.349	2.182 to 2.517	$< 10^{-4}$
Slope	0.001	-0.001 to 0.002	0.34
Intercept: Vaccinated	0.220	0.009 to 0.431	0.04
Intercept: Omicron BA1	-0.365	-0.603 to -0.128	$< 10^{-2}$
Intercept: Omicron BA2	0.112	-0.223 to 0.446	0.51
Intercept: AZD7442	**0.717**	**0.528 to 0.906**	**$< 10^{-4}$**
Slope: Vaccinated	0.002	0.000 to 0.003	0.05
Slope: Omicron BA1	-0.001	-0.003 to 0.001	0.19
Slope: Omicron BA2	0.001	-0.001 to 0.003	0.60
Slope: AZD7442	-0.002	-0.003 to -0.000	0.01

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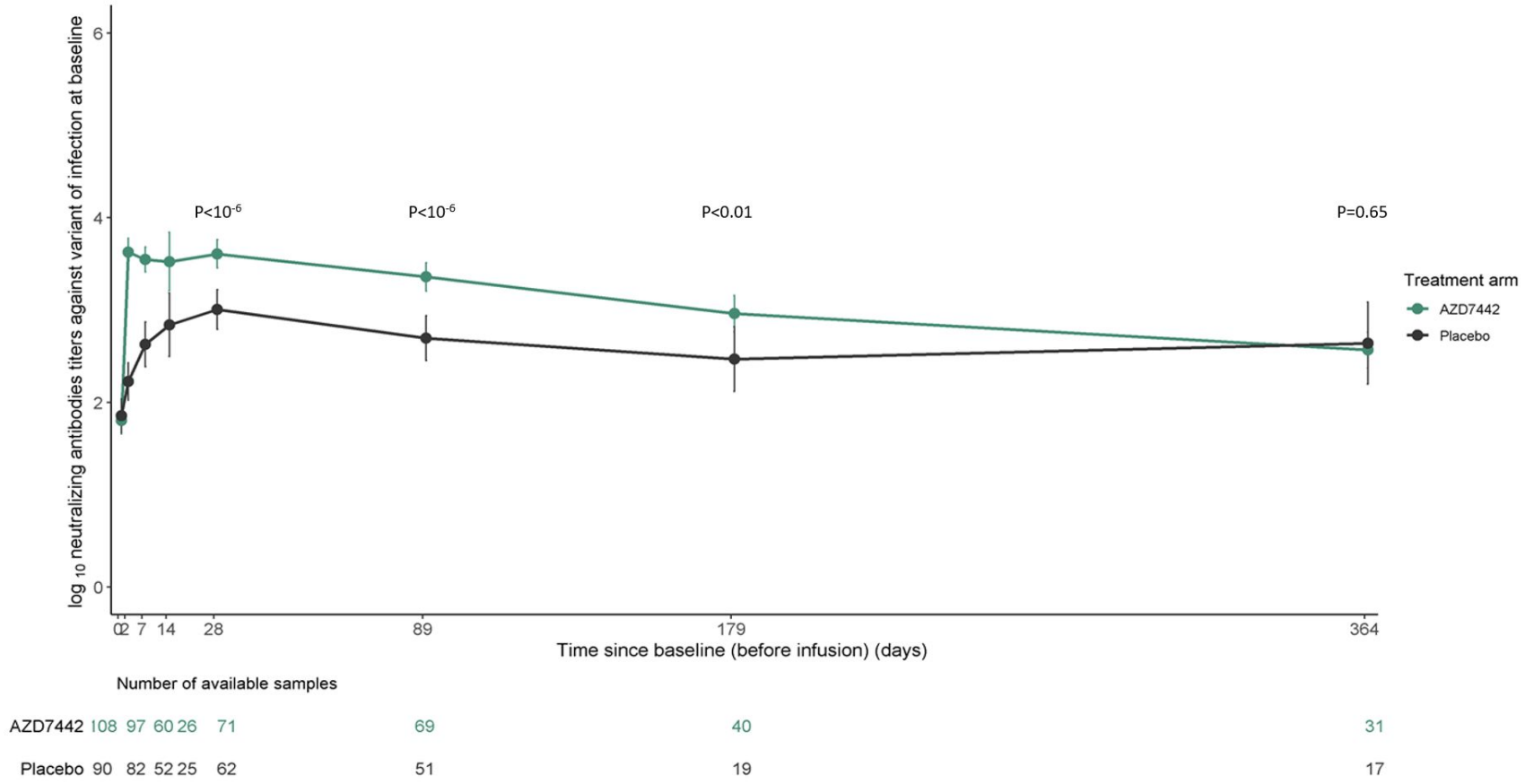
Supplementary figure 1: Neutralizing activity (mean log10 ID50 ± 95% CI) against the variant of infection, from baseline to day 365, by treatment group.



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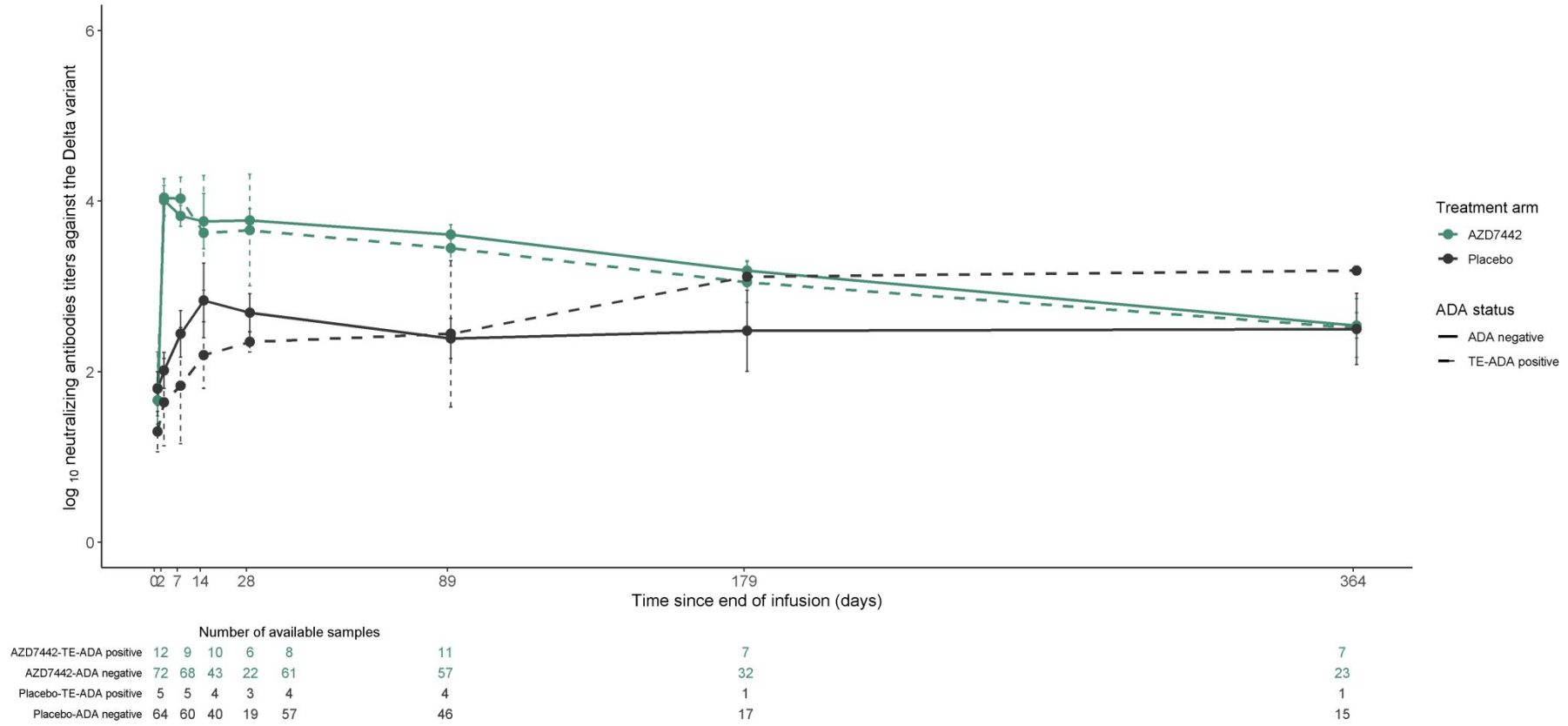
Supplementary figure 2: Neutralizing activity (mean log10 ID50 ± 95% CI) against the Delta variant, from baseline to day 365, by treatment group and anti-drug antibody (ADA) positivity status.



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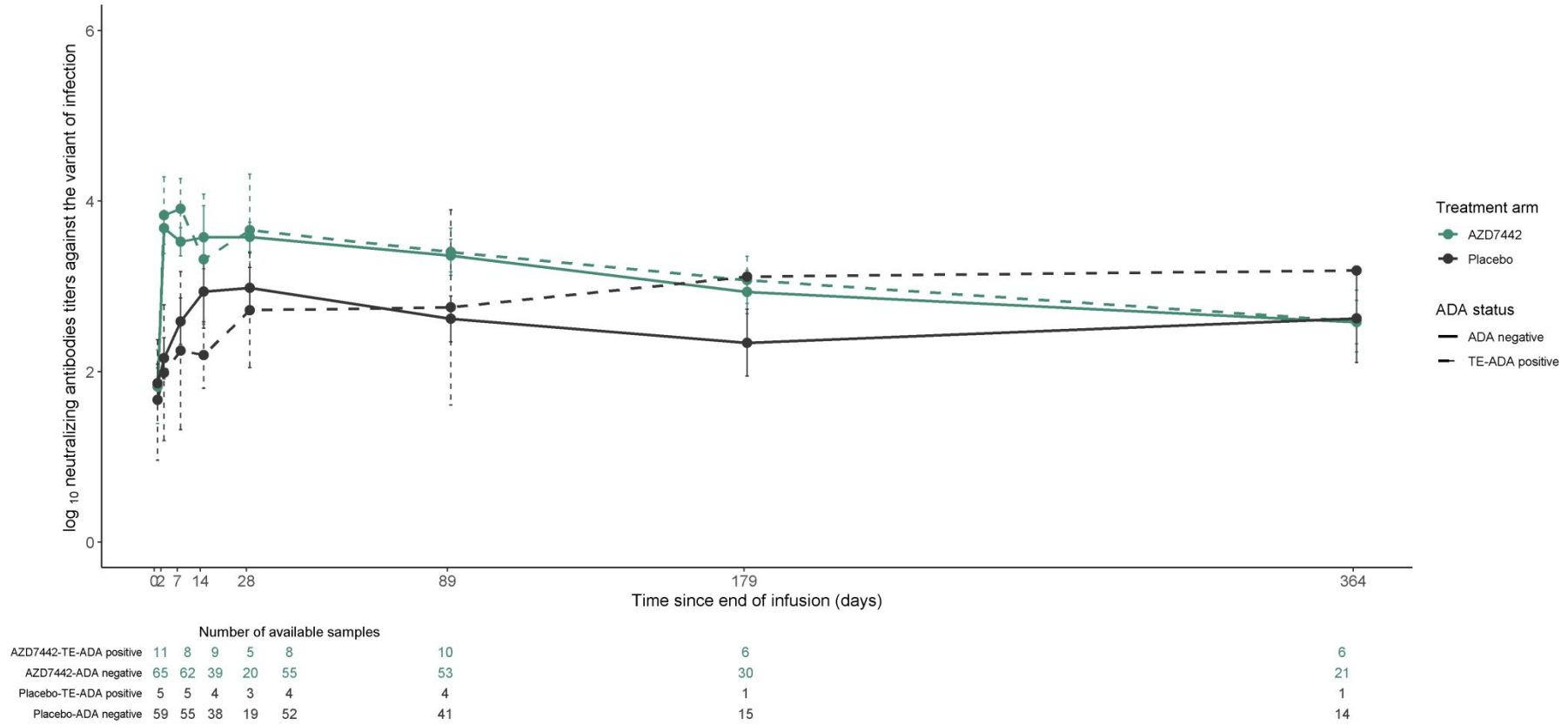
Supplementary figure 3: Neutralizing activity (mean log10 ID50 ± 95% CI) against the variant of infection, from baseline to day 365, by treatment group and anti-drug antibody (ADA) positivity status.



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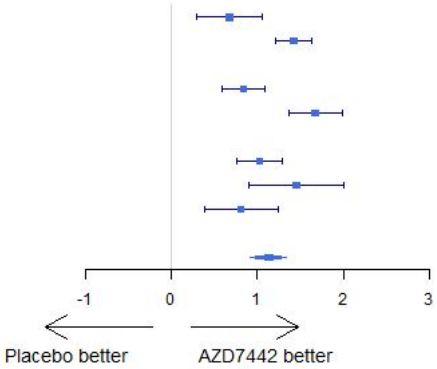
Supplementary figure 4: Titres (log10 ID50) of neutralizing antibodies targeted at the Delta variant (A) and at the variant of infection (B), on day 90, stratified by vaccination status, serology status, and variant of infection.

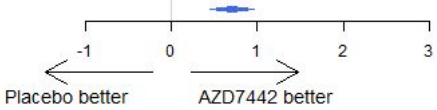
(A) Titers (log10 IC50) of neutralizing antibodies targeted at the Delta variant on Day 90

Subgroups	Number of patients	LSMD (95%CI)	P-value	P-value Interaction
Vaccination status				
Yes	53	0.67 (0.29 to 1.06)	<0.01	$< 10^{-3}$
No	77	1.42 (1.20 to 1.63)	$< 10^{-19}$	
Serology				
Positive	88	0.84 (0.58 to 1.09)	$< 10^{-8}$	$< 10^{-3}$
Negative	42	1.67 (1.36 to 1.98)	$< 10^{-11}$	
Variant of infection				
Pre-Omicron	84	1.03 (0.76 to 1.29)	$< 10^{-10}$	0.397
Omicron BA 1	27	1.45 (0.90 to 2.00)	$< 10^{-4}$	
Omicron BA 2/5	11	0.81 (0.38 to 1.24)	<0.01	
All	**130**	**1.13 (0.92 to 1.33)**	$< 10^{-18}$	



(B) Titers (log10 IC50) of neutralizing antibodies targeted at the variant of infection on Day 90

Subgroups	Number of patients	LSMD (95%CI)	P-value	P-value Interaction
Vaccination status				
Yes	49	0.12 (-0.27 to 0.51)	0.542	$< 10^{-4}$
No	71	1.17 (0.88 to 1.47)	$< 10^{-10}$	
Serology				
Positive	80	0.38 (0.08 to 0.68)	0.014	0.001
Negative	40	1.28 (0.87 to 1.69)	$< 10^{-6}$	
Variant of infection				
Pre-Omicron	84	1.03 (0.76 to 1.29)	$< 10^{-10}$	$< 10^{-4}$
Omicron BA 1	26	-0.22 (-0.90 to 0.46)	0.535	
Omicron BA 2/5	10	0.44 (-0.11 to 0.99)	0.156	
All	**120**	**0.71 (0.46 to 0.96)**	$< 10^{-6}$	



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