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Letter to the Editor

Tixagevimab-cilgavimab (AZD7442) for the treatment of patients hospitalized with COVID-19 (DisCoVeRy): A phase 3, randomized, double-blind, placebo-controlled trial

Dear Editor,

We read with great interest the recent article by Kamboj et al., in which they described the risk of developing moderate to severe Coronavirus Disease 2019 (COVID-19) in patients with hematological malignancies receiving tixagevimab-cilgavimab (T-C) during a period in which the dominant circulating variants of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) were resistant to T-C.[1] The authors highlight the ongoing need to urgently address the mAb treatment gap, particularly for immunocompromised patients. The unmet need is further highlighted by the DisCoVeRy Phase 3, adaptive, multicenter European, randomized, double-blind, superiority trial that evaluated the efficacy and safety of intravenous T-C in SARS-CoV-2 antigenic positive patients (i.e. those with a high SARS-CoV-2 viral load) hospitalized with COVID-19 and followed-up to day 90.

In the ambulatory setting, and while ancestral strains were circulating, the administration of intramuscular T-C to treat SARS-CoV-2 infections significantly reduced the risk of hospitalization and death in patients at risk for disease progression, compared to placebo.[2] In the hospital setting, the double-blinded, placebo-controlled ACTIV-3-TICO trial evaluating T-C in 1417 patients with COVID-19, with > 50% of participants infected with the Delta variant, demonstrated that treatment with T-C was associated with a 30% relative risk reduction in mortality (9% vs. 12%; hazard ratio [HR] 0.70 [95% confidence interval (CI) 0.50–0.97]; $p = 0.032$) through day 90.[3] The EU DisCoVeRy placebo-controlled trial (NCT04315948) began enrolling on April 28, 2021, after these trials were initiated (January 28, 2021, and February 10, 2021, respectively) and aimed to confirm efficacy and safety data in hospitalized COVID-19 patients during a later stage of the pandemic when the natural evolution of SARS-CoV-2 strains had led to the emergence of variants of concern (VOC), and mass vaccination campaigns had been ramped up worldwide.[4]

In DisCoVeRy, participants were randomly assigned (1:1) to receive placebo or T-C in addition to standard of care (SoC), not including remdesivir. The primary outcome was the clinical status at day 15 measured by the WHO seven-point ordinal scale. Clinical, virological, immunological and safety endpoints were also assessed.

In the context of *in-vitro* evidence showing loss of neutralization activity against emerging VOC,[5,6] enrollment slowed down until recruitment was stopped on July 1, 2022, before reaching the predetermined targeted sample size of 1240 patients. As shown in Table 1, the antigen positive modified intention-to-treat population (mITT) included 173 participants randomized to T-C ($n = 91$) or placebo ($n = 82$), among whom 91.9% (159/173) needed supplementary oxygen, 19.6% (24/173) were immunocompromised, and 47.4% (82/173) were previously vaccinated against SARS-CoV-2 at inclusion. There was no difference in the distribution of the WHO ordinal scale at day 15 between the two groups (odds ratio (OR) 0.93, 95%CI [0.54–1.61]; $p = 0.81$) nor in any clinical, virological or safety secondary endpoints (Fig. 1). In the global mITT population ($n = 226$), neutralization antibody titers were significantly higher in the T-C recipients compared to placebo at day 3 (least-square mean differences (LSMD) 1.44, 95%CI [1.20–1.68]; $p < 10^{-23}$) and day 8 (LSMD 0.91, 95%CI [0.64–1.18]; $p < 10^{-8}$) and it was greatest for patients infected with a pre-Omicron variant, both at day 3 (LSMD 1.94, 95% CI [1.67–2.20], $p < 10^{-25}$) and day 8 (LSMD 1.17, 95% CI [0.87–1.47], $p < 10^{-9}$), with a significant interaction ($p < 10^{-7}$ and $p = 0.01$ at days 3 and 8, respectively). A total of 178 adverse events (AEs), including 90 serious AEs (SAEs) were reported, of which 28 (31.1%) were considered related to the investigational medicinal product. In the T-C group, 51/123 (41.5%) patients had at least one AE, 30/123 (24.4%) had at least one grade 3 or 4 AE, and 28/123 (22.8%) had at least one SAE, against 45/103 (43.7%), 33 (32.0%), and 32 (31.1%) in the control group ($p = 0.70$, 0.18, and 0.13), respectively. Among 19 fatal SAEs, none were of cardiac origin. Complete results and all supporting documents are available on medRxiv (doi: 10.1101/2024.02.23.24302586).

Although T-C combination was safe and well-tolerated, showing no excess cardiac events, it did not significantly improve patients' clinical status in the DisCoVeRy study, nor accelerate viral clearance, despite a significant increase in neutralizing antibodies against SARS-CoV-2 at days 3 and 8 compared to placebo. The difference with the ACTIV-3-TICO trial concerning mortality is due to the underpowered nature of the DisCoVeRy trial, and possibly amongst other reasons, the changes in infecting SARS-CoV-2 variants. The Delta variant was the predominant one in both trials, but the DisCoVeRy trial enrolled 40% of patients infected with the Omicron variant compared to none in the ACTIV-3-TICO trial.[3] Indeed, the SARS-CoV-2 Omicron variant and its multiple sub-lineages have proven to be more evasive than the ancestral strain or Delta variant to vaccines and therapeutic mABs, including T-C, as assessed by *in-vitro* live-virus neutralization assays.[5,6] Infections due to the Omicron variant have overall proven to be less virulent than prior variants, including Delta,[7] however, many patients who did require hospitalization were still at risk of dying, as illustrated by the mortality rate of 15% at day 90 in our trial and the important morbidity described by Kamboj et al.[1]

The early termination of this DisCoVeRy trial, with only 19% of the planned enrollment, is an example of the difficulties to evaluate mAbs in the changing variant landscape of the COVID-19 pandemic. Due to the evolving genomics[4] as well as the increased capacity of the virus for immune escape, vulnerable individuals unable to mount an adequate immune response (e.g. the immunocompromised), remain at risk for severe COVID-19. Consequently, further reflections are needed on how best to evaluate mAbs in the clinical setting to rapidly address this

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Table 1
Baseline characteristics, clinical endpoints, and safety of participants 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	Tixagevimab-cilgavimab	Placebo	Effect measure	Overall	Tixagevimab-cilgavimab	Placebo	Effect measure
	(N = 173)	(N = 91)	(N = 82)	(95% CI)	(N = 226)	(N = 123)	(N = 103)	(95% CI)
Baseline characteristics								
Median age, years	66.0 [55.0–79.0]	65.0 [56.0–80.0]	66.5 [55.0–78.0]		66.0 [53.0–76.0]	64.0 [53.0–76.0]	68.0 [52.0–76.0]	
Sex male,	117 (67.6%)	56 (61.5%)	61 (74.4%)		155 (68.6%)	78 (63.4%)	77 (74.8%)	
Number of comorbidities*								
0	38 (22.0%)	17 (18.7%)	21 (25.6%)		52 (23.0%)	28 (22.8%)	24 (23.3%)	
1	49 (28.3%)	26 (28.6%)	23 (28.0%)		71 (31.4%)	38 (30.9%)	33 (32.0%)	
2	43 (24.9%)	23 (25.3%)	20 (24.4%)		50 (22.1%)	27 (22.0%)	23 (22.3%)	
3	25 (14.5%)	14 (15.4%)	11 (13.4%)		32 (14.2%)	18 (14.6%)	14 (13.6%)	
> 3	18 (10.4%)	11 (12.1%)	7 (8.5%)		21 (9.3%)	12 (9.8%)	9 (8.7%)	
Coexisting condition								
Chronic cardiac disease	62 (35.8%)	39 (42.9%)	23 (28.0%)		72 (31.9%)	43 (35.0%)	29 (28.2%)	
Obesity (BMI ≥ 30)	46 (26.6%)	27 (29.7%)	19 (23.2%)		63 (27.9%)	38 (30.9%)	25 (24.3%)	
Diabetes	46 (26.6%)	30 (33.0%)	16 (19.5%)		58 (25.7%)	37 (30.1%)	21 (20.4%)	
Current smoker	13 (48.1%)	6 (42.9%)	7 (53.8%)		15 (48.4%)	7 (46.7%)	8 (50.0%)	
Chronic pulmonary disease (including asthma)	43 (24.9%)	22 (24.2%)	21 (25.6%)		53 (23.5%)	27 (22.0%)	26 (25.2%)	
Active cancer (including hematological malignancy)	23 (13.3%)	9 (9.9%)	14 (17.1%)		30 (13.3%)	12 (9.8%)	18 (17.5%)	
Median days from symptoms onset and random assignment*,†*	7.0 [5.0–9.0]	7.0 [6.0–9.0]	7.0 [5.0–9.0]		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]	7.0 [5.0–9.0]		7.0 [5.0–9.0]	7.0 [5.0–8.0]	6.0 [5.0–9.0]	
Clinical status								
3. Hospitalized, not requiring supplemental oxygen	7 (4.0%)	5 (5.5%)	2 (2.4%)		9 (4.0%)	6 (4.9%)	3 (2.9%)	
4. Hospitalized, requiring supplemental oxygen	141 (81.5%)	71 (78.0%)	70 (85.4%)		179 (79.2%)	93 (75.6%)	86 (83.5%)	
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	25 (14.5%)	15 (16.5%)	10 (12.2%)		38 (16.8%)	24 (19.5%)	14 (13.6%)	
Randomization site								
Intensive care unit	21 (12.1%)	15 (16.5%)	6 (7.3%)		32 (14.2%)	21 (17.1%)	11 (10.7%)	
Conventional unit	152 (87.9%)	76 (83.5%)	76 (92.7%)		194 (85.8%)	102 (82.9%)	92 (89.3%)	
Vaccination initiation (partly or fully)	82 (47.4%)	43 (47.3%)	39 (47.6%)		102 (45.1%)	56 (45.5%)	46 (44.7%)	
Serology*								
Negative (anti-N antibodies -and anti-S RBD antibodies -)	69 (40.4%)	40 (44.4%)	29 (35.8%)		76 (34.4%)	44 (36.4%)	32 (32.0%)	
Positive (anti-N antibodies + or anti-S RBD antibodies +)	102 (59.6%)	50 (55.6%)	52 (64.2%)		145 (65.6%)	77 (63.6%)	68 (68.0%)	
Variant Omicron on day 1 (imputed)*								
Pre-Omicron	99 (57.2%)	52 (57.1%)	47 (57.3%)		133 (58.8%)	70 (56.9%)	63 (61.2%)	
Omicron BA1	44 (25.4%)	25 (27.5%)	19 (23.2%)		53 (23.5%)	32 (26.0%)	21 (20.4%)	
Omicron BA2/5	20 (11.6%)	10 (11.0%)	10 (12.2%)		22 (9.7%)	11 (8.9%)	11 (10.7%)	
Unknown	10 (5.8%)	4 (4.4%)	6 (7.3%)		18 (8.0%)	10 (8.1%)	8 (7.8%)	
Median normalized viral load in nasopharyngeal swabs at baseline, log_{10} copies per 10,000 cells‡	4.4 [3.3–5.4]	4.4 [3.4–5.3]	4.4 [3.3–5.6]		4.0 [2.5–5.2]	3.9 [2.4–5.1]	4.1 [2.7–5.3]	

(*continued on next page*)

Table 1 (*continued*)

	Antigen positive (N = 173)				Global (N = 226)			
	Overall	Tixagevimab-cilgavimab	Placebo	Effect measure	Overall	Tixagevimab-cilgavimab	Placebo	Effect measure
	(N = 173)	(N = 91)	(N = 82)	(95% CI)	(N = 226)	(N = 123)	(N = 103)	(95% CI)
Clinical endpoints								
7-point ordinal scale at day 15								
1. Not hospitalized, no limitations on activities	35 (20.2%)	15 (16.5%)	20 (24.4%)	OR = 0.93 (0.54–1.61)	48 (21.2%)	20 (16.3%)	28 (27.2%)	OR = 0.85 (0.52–1.37)
2. Not hospitalized, limitation on activities	77 (44.5%)	45 (49.5%)	32 (39.0%)	[p = 0.81]	104 (46.0%)	63 (51.2%)	41 (39.8%)	[p = 0.50]
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%)		13 (5.8%)	10 (8.1%)	3 (2.9%)	
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%)	
Time to sustained recovery through day 90 (days)	22.0 [19.0–27.0]	22.0 [19.0–27.5]	21.0 [18.0–27.0]	HR = 0.98 (0.71–1.36) [p = 0.92]	21.0 [18.0–27.0]	22.0 [19.0–27.5]	21.0 [18.0–27.0]	HR = 1.01 (0.77–1.34) [p = 0.93]
Days to hospital discharge before day 90	8.0 [6.0–13.0]	8.0 [6.0–11.0]	9.0 [5.0–13.0]	HR = 1.06 (0.78–1.45) [p = 0.70]	8.0 [5.0–13.0]	8.0 [5.0–12.0]	8.0 [5.0–13.0]	HR = 1.10 (0.84–1.43) [p = 0.49]
Mortality rate at day 90	26 (15.0%)	12 (13.2%)	14 (17.1%)	OR = 0.73 (0.31–1.72) [p = 0.47]	28 (12.4%)	12 (9.8%)	16 (15.5%)	OR = 0.56 (0.25–1.28) [p = 0.17]
Safety								
Number of patients with at least one adverse event								
Any adverse events					96 (42.5%)	51 (41.5%)	45 (43.7%)	OR = 0.90 (0.53–1.54) [p = 0.70]
Any grade 1 adverse events					20 (8.8%)	12 (9.8%)	8 (7.8%)	
Any grade 2 adverse events					29 (12.8%)	18 (14.6%)	11 (10.7%)	
Any grade 3 adverse events					34 (15.0%)	18 (14.6%)	16 (15.5%)	
Any grade 4 adverse events					35 (15.5%)	14 (11.4%)	21 (20.4%)	
Any grade 1 and 2 adverse events					43 (19.0%)	25 (20.3%)	18 (17.5%)	
Any grade 3 and 4 adverse events					63 (27.9%)	30 (24.4%)	33 (32.0%)	OR = 0.67 (0.37–1.20) [p = 0.18]
Number of patients with at least one serious adverse event								
Any serious adverse events					60 (26.5%)	28 (22.8%)	32 (31.1%)	OR = 0.63 (0.35–1.15) [p = 0.13]
Any serious adverse events leading to outcome of death					19 (8.4%)	9 (7.3%)	10 (9.7%)	

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

Analyses were stratified on the vaccination status at randomization and adjusted effect measures are reported in the table. For the ordinal scale results, an odds ratio above 1 is in the direction of tixagevimab-cilgavimab being better than placebo. For time to event analyses, a hazard ratio above 1 is in the direction of tixagevimab-cilgavimab being better than placebo. Estimates are reported with their 95% confidence interval. As per the definition in the protocol, adverse events and serious adverse events do not include disease-related events. CI: confidence interval; OR: odds ratio; HR: hazard ratio; BMI: body mass index; ECMO: extracorporeal membrane oxygenation.

* Denotes variables with missing data. The number of missing data is presented for the antigen positive/the global mITT for each variable, respectively. Data on smoking status (current) were missing in 3/3 participants; data on delay between first laboratory-confirmed SARS-CoV-2 infection and admission date at facility were missing in 1/1 participant; data on delay between first laboratory-confirmed SARS-CoV-2 infection and randomization were missing in 1/1 participant; data on serology test were missing on 2/5 participants; data on variant sequencing were missing in 35/71 participants; data on body weight were missing on 10/11 participants; data on NEWS2 score were missing on 16/20 participants.

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

‡ Undetectable viral load values (i.e. values < 1 $\log_{10}$ copies/10 000 cells) were imputed to 0.7 $\log_{10}$ copies/10 000 cells.

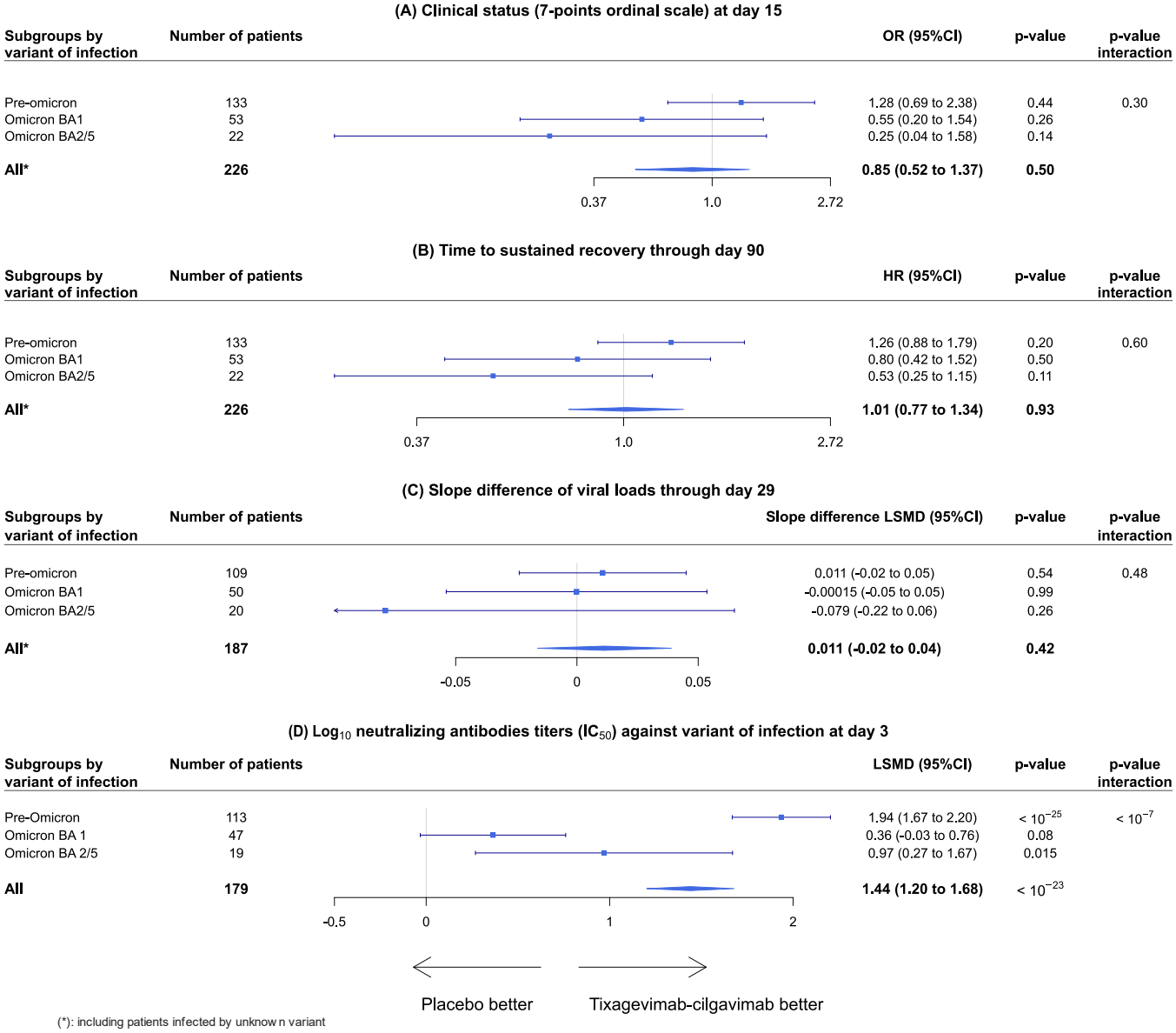

Fig. 1. Forest plots of subgroup analyses according to the variant of infection, for the (A) clinical status (7-points ordinal scale) at day 15, (B) time to sustained recovery through day 90, (C) slope difference of viral loads through day 29, (D) $\log_{10}$ neutralizing antibody titers against variant of infection at day 3, in patients from the global modified intention-to-treat population.

urgent unmet need by bringing new therapeutic options to patients, particularly immunocompromised, while ensuring their safety. Novel approaches for evaluating mAbs include immuno-bridging trials, where humoral and/or cellular immune parameters are evaluated in a controlled trial to establish whether an intervention is effective[8] and the adoption of a global surveillance system with criteria for *in-vitro* evaluation of antiviral susceptibility correlated to clinical data.[9] Modeling antiviral effects while accounting for vaccination status, SARS-CoV-2 antibody levels, infecting viral strains, and other parameters, may provide better insight into antiviral efficacy of mAbs, as we have previously shown with remdesivir.[10]

Declaration of Competing Interest

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