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

Maya Hites
Clément R. Massonnaud
Simon Jamard
François Goehringer
François Danion
Jean Reignier
Nathalie de Castro
Denis Garot
Eva Larranaga Lapique
Karine Lacombe
Violaine Tolsma
Emmanuel Faure
Denis Malvy
Thérèse Staub
Johan Courjon
France Cazenave-Roblot
Anne Ma Dyrhol Riise
Paul Leturnier
Guillaume Martin-Blondel
Claire Roger
Karolina Akinosoglou
Vincent Le Moing
Lionel Piroth
Pierre Sellier
Xavier Lescure
Marius Trøseid
Philippe Clevenbergh
Olav Dalgard
Sébastien Gallien
Marie Gousseff
Paul Loubet
Fanny Vardon-Bounes
Clotilde Visée
Leila Belkhir
Élisabeth Botelho-Nevers
André Cabié
Anastasia Kotanidou
Fanny Lanternier
Elisabeth Rouveix-Nordon
Susana Silva
Guillaume Thiery
Pascal Poignard



Guislaine Carcelain
Alpha Diallo, Noémie Mercier, Vida Terzic
Maude Bouscambert-Duchamp, Alexandre
Gaymard
Mary-Anne Trabaud
Grégory Destras, Laurence Josset
Drifa Belhadi
Nicolas Billard
Jérémi Guedj
Thi-Hong-Lien Han
Sandrine Couffin-Cadiergues
Aline Dechanet
Christelle Delmas, Hélène Esperou
Claire Fougerou-Leurent
Soizic Le Mestre
Anabelle Métois
Marion Noret
Isabelle Bally, Sebastián Dergan-Dylon
Sarah Tubiana
Ouifiya Kalif
Nathalie Bergaud, Benjamin Leveau
Joe Eustace
Richard Greil
Edit Hajdu
Monika Halanova
Jose-Artur Paiva
Anna Piekarska
Jesus Rodriguez Baño
Kristian Tonby
Milan Trojáněk
Sotirios Tsiodras
Serhat Unal
Charles Burdet
Dominique Costagliola
Yazdan Yazdanpanah
Nathan Peiffer-Smadja
France Mentré
Florence Ader

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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

Prof. Maya Hites, MD,^{1*} Clément R. Massonnaud, MD,^{2,3*} Simon Jamard, MD,⁴ François Goehringer, MD,⁵ François Danion, MD,⁶ Prof. Jean Reignier, MD,⁷ Nathalie de Castro, MD,⁸ Denis Garot, MD,⁹ Eva Larranaga Lapique, MD,¹ Prof. Karine Lacombe, MD,^{10,11} Violaine Tolsma, MD,¹² Emmanuel Faure, MD,¹³ Prof. Denis Malvy, MD,¹⁴ Prof. Thérèse Staub, MD,¹⁵ Johan Courjon, MD,¹⁶ Prof. France Cazenave-Roblot, MD,¹⁷ Anne Ma Dyrhol Riise, MD,¹⁸ Paul Leturnier, MD,¹⁹ Prof. Guillaume Martin-Blondel, MD,^{20,21} Claire Roger, MD,²² Karolina Akinosoglou, MD,²³ Prof. Vincent Le Moing, MD,²⁴ Lionel Piroth, MD,^{25,26} Pierre Sellier, MD,²⁷ Prof. Xavier Lescure, MD,^{3,28} Marius Trøseid, MD,²⁹ Philippe Clevenbergh, MD,³⁰ Olav Dalgard, MD,^{31,32} Prof. Sébastien Gallien, MD,^{33,34} Marie Gousseff, MD,³⁵ Paul Loubet, MD,^{36,37} Fanny Vardon-Boune, MD,^{38,39} Clotilde Visée, MD,⁴⁰ Leila Belkhir, MD,⁴¹ Prof. Élisabeth Botelho-Nevers, MD,⁴²⁻⁴⁴ Prof. André Cabié, MD,^{45,46} Anastasia Kotanidou, MD,⁴⁷ Fanny Lanternier, MD,⁴⁸ Elisabeth Rouveix-Nordon, MD,⁴⁹ Susana Silva, MD,⁵⁰ Guillaume Thiery, MD,⁵¹ Prof. Pascal Poignard, MD,⁵²⁻⁵⁴ Prof. Guislaine Carcelain, MD,^{55,56} Alpha Diallo, MD,⁵⁷ Noémie Mercier, MSc,⁵⁷ Vida Terzic,⁵⁷ Maude Bouscambert-Duchamp, PharmD,^{58,59} Alexandre Gaymard, PharmD,^{58,59} Mary-Anne Trabaud, PhD,⁶⁰ Grégory Destras, PharmD,⁵⁸ Laurence Josset, PharmD,⁵⁸ Drifa Belhadi, MSc,^{2,3} Nicolas Billard,² Jérémie Guedj, PhD,³ Thi-Hong-Lien Han, MSc,² Sandrine Couffin-Cadiergues,⁶¹ Aline Dechanet, MSc,⁶² Christelle Delmas, MSc,⁶¹ Hélène Esperou, MD,⁶¹ Claire Fougrou-Leurent, PharmD,⁶³ Soizic Le Mestre,⁵⁷ Anabelle Métois,⁶² Marion Noret,⁶⁴ Isabelle Bally,⁵³ Sebastián Dergan-Dylon,⁵³ Sarah Tubiana, PharmD,^{3,65} Ouifiya Kalif,⁶⁵ Nathalie Bergaud,⁶⁶ Benjamin Leveau,⁶⁶ Prof. Joe Eustace, MD,⁶⁷ Prof. Richard Greil, MD,⁶⁸⁻⁷⁰ Prof. Edit Hajdu, MD,⁷¹ Prof. Monika Halanova, MVD, ⁷² Prof. Jose-Artur Paiva, MD,^{73,74} Prof. Anna Piekarska, MD,⁷⁵ Prof. Jesus Rodriguez Baño, MD,⁷⁶ Prof. Kristian Tonby, MD,¹⁸ Milan Trojáněk, MD,⁷⁷ Prof. Sotirios Tsiodras, MD,⁷⁸ Prof. Serhat Unal, MD,⁷⁹ Charles Burdet, MD,^{2,3} Dominique Costagliola, PhD,¹⁰ Prof. Yazdan Yazdanpanah, MD,^{3,28} Nathan Peiffer-Smadja, MD,^{3,28,80} Prof. France Mentré, MD,^{2,3**} Prof. Florence Ader, MD,^{81,82**}

on behalf of the DisCoVeRy study group

* co-first authors

** co-last authors

Corresponding author

Maya Hites, M.D., Ph.D., Clinique des maladies infectieuses, Hôpital Universitaire de Bruxelles, 808 Route de Lennik, 1070 Belgique
Tel : 00.32.2.555.5779/ Fax : 00.32.2.555.3912
e-mail : Maya.Hites@hubruxelles.be

Author affiliations

1. Clinic of Infectious Diseases, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles, Brussels, Belgium.
2. AP-HP, Hôpital Bichat, Département d'Épidémiologie, Biostatistique et Recherche Clinique, F-75018 Paris, France.
3. Université de Paris, IAME, INSERM, F-75018 Paris, France.
4. Service de Maladies Infectieuses Et Tropicales (SMIT), Centre Hospitalier Universitaire de Tours, 37044, Tours, France.
5. Université de Lorraine, CHRU de Nancy, Service des Maladies Infectieuses et Tropicales, F-54000 Nancy, France.
6. Hôpitaux Universitaires de Strasbourg, Département de maladies infectieuses et tropicales, F-67091 Strasbourg. France.
7. CHU de Nantes, Service de Médecine Intensive et Réanimation, Université de Nantes, F-44093 Nantes, France.
8. Département des Maladies Infectieuses et Tropicales, GH Saint-Louis/Lariboisière-Fernand Widal, Université de Paris Cité, INSERM U 944.
9. CHRU Tours, Service de Médecine Intensive Réanimation, F-37044 Tours, France.
10. Sorbonne Université, Inserm, Institut Pierre-Louis d'Épidémiologie et de Santé Publique, F-75013, Paris, France.
11. APHP, Hôpital Saint-Antoine, Service de maladies infectieuses et tropicales, F-75012 Paris, France.
12. Centre Hospitalier Annecy Genevois, Service des Maladies Infectieuses et Tropicales, F-74374 Annecy, France.
13. Université de Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, U1019 - UMR 9017 - CIIL - Center for Infection and Immunity of Lille, F-59000 Lille, France.
14. Department of Infectious Diseases and Tropical Medicine, CHU Bordeaux, Bordeaux, France.
15. Centre hospitalier de Luxembourg, Service des maladies infectieuses, L-1210 Luxembourg, Luxembourg.
16. Université Côte d'Azur, CHU Nice, Nice, France, Infectious Disease Unit, Nice, France.
17. Département des Maladies Infectieuses et Tropicales, CHU de Poitiers, INSERM U1070, Poitiers, France.
18. Department of Infectious Diseases, Oslo University Hospital, 0424 Oslo, Norway.
19. Department of Infectious Diseases, Hôtel-Dieu University Hospital, University Hospital of Nantes, Nantes, France.
20. CHU de Toulouse, Service des maladies infectieuses et Tropicales, F-31320 Toulouse, France.

21. Institut Toulousain des Maladies Infectieuses et Inflammatoires (Infinity) INSERM UMR1291 - CNRS UMR5051 - Université Toulouse III, F-31320 Toulouse, France.
22. Department of Anesthesiology, Critical Care Pain, and Emergency Medicine, Nimes University Hospital, Nimes, France.
23. Department of Internal Medicine and Infectious Diseases, University General Hospital of Patras, Patras, Greece.
24. CHU de Montpellier, Service des Maladies Infectieuses et Tropicales, F- 34295 Montpellier, France.
25. CHU de Dijon, Département de Maladies Infectieuses, F-21000, Dijon, France.
26. Université Bourgogne Franche-Comté, CIC 1432, INSERM, F-21000, Dijon, France.
27. Infectious Diseases Department, Lariboisière Hospital, AP-HP, Paris, France.
28. AP-HP, Hôpital Bichat, Service de Maladies Infectieuses et Tropicales, F-75018 Paris, France.
29. Research Institute of Internal Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital Rikshospitalet, Oslo, Norway.
30. Infectious Diseases Clinic, CHU Brugmann, ULB, Brussels, Belgium.
31. Department of Infectious Diseases, Division of Medicine, Akershus University Hospital, Lørenskog, Norway.
32. Institute for Clinical Medicine, University of Oslo, Norway.
33. APHP, Hôpital Henri Mondor, Département de maladies infectieuses, F-94000 Créteil, France.
34. INSERM U955, Team 16, IMRB Créteil, Créteil, France.
35. Maladies infectieuses, Centre Hospitalier Bretagne-Atlantique, Vannes, France.
36. Infectious and Tropical Diseases Department, Nimes University Hospital, Nimes, France.
37. VBIC, INSERM U1047, University of Montpellier, Nimes, France.
38. CHU de Toulouse, Département d'anesthésie et de soins intensifs, F- 31300 Toulouse, France.
39. Université Toulouse 3 Paul Sabatier, Inserm U1297, F- 31300 Toulouse, France.
40. Department of Infectious Disease, Centre Hospitalier Régional Mons-Hainaut/Groupe Jolimont, Mons Belgium/Groupe Helora, Mons, Belgium.
41. Department of Internal Medicine and Infectious Diseases, Cliniques universitaires Saint-Luc, Brussels, Belgium.
42. CHU de Saint-Etienne, Service d'Infectiologie, F- 42055 Saint-Etienne, France.
43. Université Jean Monnet, Université Claude Bernard Lyon 1, GIMAP, CIRI, INSERM U1111, CNRS UMR5308, ENS Lyon, F-42023 Saint-Etienne, France.
44. CIC 1408, INSERM, F- 42055 Saint-Etienne, France.
45. PCCEI, Univ Montpellier, Univ Antilles, Inserm, EFS, F- 34394 Montpellier, France.

46. CHU de Martinique, Service des maladies infectieuses et tropicales, Inserm CIC1424, F- 97200 Fort de France, France.
47. First Department of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, National and Kapodistrian University of Athens Medical School, 45-47 Ipsilantou Street, 10676, Athens, Greece.
48. Infectious Diseases Unit, Necker-Enfants Malades University Hospital, AP-HP, Paris, France.
49. AP-HP, Hôpital Ambroise-Paré, Service de Maladies Infectieuses et Tropicales, Boulogne-Billancourt, France.
50. EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, n° 135, 4050-600, Porto, Portugal.
51. CHU Saint-Etienne, Hopital Nord, Medical Intensive Care Unit, Saint-Priest-En-Jarez, France.
52. Groupe de Recherche en Infectiologie Clinique CIC-1406, Inserm - CHUGA - Université Grenoble Alpes, Grenoble, France.
53. Univ. Grenoble Alpes, CEA, CNRS, Institut de Biologie Structurale (IBS), Grenoble, France.
54. Laboratoire de Virologie, Center Hospitalier Universitaire Grenoble-Alpes, Grenoble, France.
55. Immunology Department, Robert Debré Hospital, Assistance Publique Hôpitaux de Paris, Paris, France.
56. Université Paris Cité, INSERM U976, Paris, France.
57. ANRS | Maladies Infectieuses Emergentes, Paris, France.
58. Hospices Civils de Lyon, Laboratoire de Virologie, Institut des Agents Infectieux de Lyon, Centre National de Référence des virus respiratoires France Sud, F-69317, Lyon, France.
59. Université Claude Bernard Lyon 1, Virpath, CIRI, INSERM U1111, CNRS UMR5308, ENS Lyon, F-69372, Lyon, France.
60. Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France.
61. Institut de santé publique, Pôle recherche clinique, INSERM, Paris, France.
62. AP-HP, Hôpital Bichat, Unité de recherche clinique, F-75018 Paris, France.
63. CHU de Rennes, Université Rennes 1, Inserm CIC 1414, F-35000 Rennes, France.
64. Renarci, Réseau National De Recherche Clinique En Infectiologie, France.
65. AP-HP, Hôpital Bichat, Centre de ressources biologiques, F-75018 Paris, France.
66. Hospices Civils de Lyon, Lyon, France.
67. University College Cork, Cork, Ireland.
68. Department of Internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, Oncologic Center, Salzburg Cancer Research Institute - Laboratory for

Immunological and Molecular Cancer Research (SCRI-LIMCR), Paracelsus Medical University Salzburg, 5020 Salzburg, Austria.

69. Cancer Cluster Salzburg, 5020, Salzburg, Austria.
70. AGMT, 5020 Salzburg, Austria.
71. Department of Internal Medicine Infectiology Unit, Albert Szent-Györgyi Health Centre, University of Szeged, Állomás Street 1-3, 6725 Szeged, Hungary.
72. LF UPJŠ - Pavol Jozef Šafárik University in Košice Faculty of Medicine.
73. Centro Hospitalar São João, Emergency and Intensive Care Department, Porto, Portugal.
74. Universidade do Porto, Faculty of Medicine, Porto, Portugal.
75. Department of Infectious Diseases and Hepatology, Medical University of Łódź, Łódź, Poland.
76. Infectious Diseases and Microbiology Division, Hospital Universitario Virgen Macarena, Sevilla, Spain.
77. Department of Infectious Diseases, University Hospital Bulovka, Budínova 2, 180 81, Prague, Czech Republic.
78. Fourth Department of Internal Medicine, Attikon University Hospital, Athens Medical School, National and Kapodistrian University of Athens, 12462 Athens, Greece.
79. Department of Infectious Diseases, Hacettepe University Faculty of Medicine, Ankara, Turkey.
80. National Institute for Health Research, Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK.
81. Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Département des Maladies Infectieuses et Tropicales, F-69004, Lyon, France.
82. Université Claude Bernard Lyon 1, CIRI, INSERM U1111, CNRS UMR5308, ENS Lyon, F-69372, Lyon, France.

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, multicentre 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%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} enrolment slowed down until recruitment was stopped on July 1, 2022 before reaching the pre-determined 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 (Figure

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% Confidence interval (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.

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 enrolment, is an example of the difficulties to evaluate mABs in the changing variant landscape of the COVID-19 pandemic. Due to the evolving genomics⁴ 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 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 effective⁸ and the adoption of a global surveillance system with criteria for *in-vitro* evaluation of antiviral susceptibility correlated to clinical data.⁹ Modelling 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

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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 (N=173)	Tixagevimab-cilgavimab (N=91)	Placebo (N=82)	Effect measure (95% CI)	Overall (N=226)	Tixagevimab-cilgavimab (N=123)	Placebo (N=103)	Effect measure (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%)	

	Antigen positive (N=173)				Global (N=226)			
	Overall (N=173)	Tixagevimab- cilgavimab (N=91)	Placebo (N=82)	Effect measure (95% CI)	Overall (N=226)	Tixagevimab- cilgavimab (N=123)	Placebo (N=103)	Effect measure (95% CI)
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%)	
Randomisation 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, log₁₀ copies per 10000 cells	4.4 [3.4-5.4]	4.4 [3.5-5.3]	4.5 [3.4-5.6]		4.2 [3.0-5.3]	4.2 [2.8-5.2]	4.2 [3.3-5.4]	
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%)		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%)	
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 to 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 to 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 to 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 to 1.43) [P=0.49]
Mortality rate at Day 90	26 (15.0%)	12 (13.2%)	14 (17.1%)	OR=0.73 (0.31 to 1.72) [P=0.47]	28 (12.4%)	12 (9.8%)	16 (15.5%)	OR=0.56 (0.25 to 1.28) [P=0.17]
Safety								
Number of patients with at least one adverse event (excluding DRE)								
Any adverse events (excluding DRE)					96 (42.5%)	51 (41.5%)	45 (43.7%)	OR=0.90 (0.53 to 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 to 1.20) [P=0.18]
Number of patients with at least one serious adverse event (excluding DRE)								

	Antigen positive (N=173)			Global (N=226)				
	Overall (N=173)	Tixagevimab- cilgavimab (N=91)	Placebo (N=82)	Effect measure (95% CI)	Overall (N=226)	Tixagevimab- cilgavimab (N=123)	Placebo (N=103)	Effect measure (95% CI)
Any serious adverse events					60 (26.5%)	28 (22.8%)	32 (31.1%)	OR=0.63 (0.35 to 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(%). HIV: human immunodeficiency virus.

* 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.

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 new invasive mechanical ventilation use during the first 29 days, a hazard ratio below 1 is in the direction of tixagevimab-cilgavimab being better than placebo. For other time to event analyses, a hazard ratio above 1 is in the direction of tixagevimab-cilgavimab being better than placebo. ECMO, extracorporeal membrane oxygenation; OR, Odds ratio; HR, Hazard ratio; LSMD, least-square mean difference. DRE: disease related event. Estimates are reported with their 95% confidence interval.

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Declaration of interests

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Figure 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 (in days), (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.

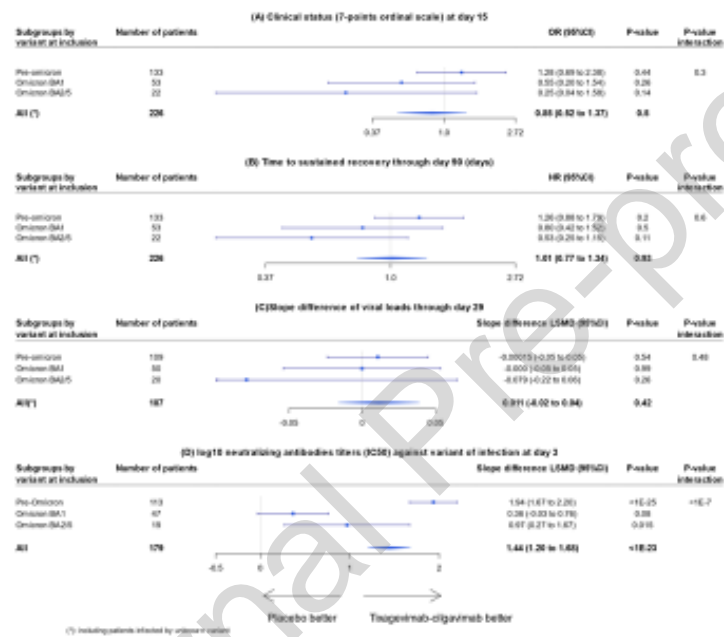


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