Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cardiac and vascular serious adverse events following tixagevimab–cilgavimab

Author's reply

We thank Jolanta Piszczek and colleagues for their meta-analysis of cardiac and vascular serious adverse events; however, this definition differs from how they were reported in the cited clinical studies, which refer to separate system organ class terms for "cardiac disorders" and "vascular disorders" (defined by Medical Dictionary for Regulatory Activities [MedDRA] 24.0) and should not be combined in an analysis.

We report further on cardiac and vascular serious adverse events from ongoing AstraZeneca-sponsored phase 3 trials with updated data cutoffs, showing distribution across individual events and lack of common pathology (table). Most vascular events were not thrombosis-related. Although more participants in PROVENT experienced cardiac serious adverse events with 300 mg tixagevimab–cilgavimab versus placebo, this imbalance was not observed in STORM CHASER, nor with the higher 600 mg dose in TACKLE in the treatment group, with no clear temporal pattern following dosing. All participants who experienced cardiac serious adverse events were high-risk and had at least one baseline cardiovascular risk factor, or history of cardiac events. No cardiac serious adverse events were observed in a phase 1 study (doses up to 3000 mg), indicating absence of dose association. No causal relationship was established.[3]

Safety evaluation continues in ongoing trials and post-marketing surveillance. We searched the AstraZeneca safety database (the largest tixagevimab–cilgavimab post-marketing surveillance safety dataset) up to June 30, 2022, using MedDRA (version 25.0), system organ class term "cardiac disorder". With an estimated 1 515 812 doses of 300 mg tixagevimab–cilgavimab distributed for COVID-19 prevention

	PROVENT*		STORM CHASER†		TACKLE‡	
	Tixagevimab–cilgavimab (n=3461)	Placebo (n=1736)	Tixagevimab–cilgavimab (n=749)	Placebo (n=372)	Tixagevimab–cilgavimab (n=452)	Placebo (n=451)
Participants with cardiac serious adverse events	38 (1·1%)	8 (0·5%)	2 (0·3%)	2 (0·5%)	3 (0·7%)	3 (0·7%)
Acute myocardial infarction	6 (0·2%)	3 (0·2%)	0	1 (0·3%)	2 (0·4%)	0
Myocardial infarction	8 (0·2%)	1 (0·1%)	1 (0·1%)	0	0	0
Cardiac failure congestive	6 (0·2%)	0	0	0	0	0
Atrial fibrillation	3 (0·1%)	2 (0·1%)	0	0	0	0
Coronary artery disease	2 (0·1%)	1 (0·1%)	0	1 (0·3%)	0	0
Acute left ventricular failure	1 (<0·1%)	1 (0·1%)	0	0	1 (0·2%)	0
Angina unstable	2 (0·1%)	0	0	0	0	0
Arteriosclerosis coronary artery	1 (<0·1%)	1 (0·1%)	0	0	0	0
Angina pectoris	1 (<0·1%)	0	0	0	0	0
Arrhythmia	1 (<0·1%)	0	0	0	0	2 (0·4%)
Atrioventricular block complete	1 (<0·1%)	0	0	0	0	0
Bradycardia	1 (<0·1%)	0	0	0	0	0
Cardiac arrest	0	0	1 (0·1%)	0	0	0
Cardiac failure	1 (<0·1%)	0	1 (0·1%)	0	0	1 (0·2%)
Cardiac failure acute	1 (<0·1%)	0	0	0	0	0
Cardio-respiratory arrest	1 (<0·1%)	0	0	0	0	0
Cardiogenic shock	1 (<0·1%)	0	0	0	0	0
Cardiomegaly	1 (<0·1%)	0	0	0	0	0
Cardiomyopathy	1 (<0·1%)	0	0	0	0	0
Left ventricular failure	1 (<0·1%)	0	0	0	0	0
Mitral valve disease	1 (<0·1%)	0	0	0	0	0
Paroxysmal atrioventricular block	1 (<0·1%)	0	0	0	0	0
Stress cardiomyopathy	0	1 (0·1%)	0	0	0	0
Ventricular arrhythmia	1 (<0·1%)	0	0	0	0	0
Sudden cardiac death§	0	0	0	0	1 (0·2%)	0
Participants with vascular serious adverse events	8 (0·2%)	5 (0·3%)	0	0	2 (0·4%)	0
Hypertension	6 (0·2%)	0	0	0	0	0
Hypotension	1 (<0·1%)	2 (0·1%)	0	0	0	0
Aortic aneurysm	0	1 (0·1%)	0	0	0	0
Deep vein thrombosis	1 (<0·1%)	0	0	0	0	0
Hypertensive crisis	0	0	0	0	1 (0·2%)	0
Hypertensive urgency	0	1 (0·1%)	0	0	0	0
Peripheral artery thrombosis	0	0	0	0	1 (0·2%)	0
Shock haemorrhagic	0	1 (0·1%)	0	0	0	0

Data are n (%). MedDRA=Medical Dictionary for Regulatory Activities. *Median follow up of 414 days for tixagevimab–cilgavimab and 413 days for placebo; data cutoff April 13, 2022. †Median follow up of 405 days for tixagevimab–cilgavimab and 402 days for placebo; data cutoff April 4, 2022. ‡Median follow up of 170 days for both tixagevimab–cilgavimab and placebo; data cutoff Jan 14, 2022. §Sudden cardiac death was reported under system organ class "general disorders and administration site conditions". Available data presented for PROVENT and TACKLE studies beyond published follow-up periods.[1,2] Some participants had more than one cardiac or vascular serious adverse event; participants with multiple events of the same system organ class are counted only once in that system organ class. In PROVENT, one participant in the tixagevimab–cilgavimab arm experienced both cardiac and vascular serious adverse event. Cardiac and vascular serious adverse events categorised by MedDRA system organ class as "cardiac disorders" and "vascular disorders" and preferred terms using MedDRA version 24.0. Serious adverse events were defined in study protocols as an adverse event occurring during any study phase (ie, run-in, treatment, washout, or follow-up) that fulfils one or more of the following criteria: results in death; is immediately life-threatening; requires in-participant hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital abnormality or birth defect; or is an important medical event that could jeopardise the participant or might require medical treatment to prevent one of the listed outcomes.

Table: **Cardiac and vascular serious adverse events occurring in AstraZeneca-sponsored phase 3 trials of tixagevimab–cilgavimab**

Published Online
December 12, 2022
https://doi.org/10.1016/
S2213-2600(22)00450-7

in immunocompromised individuals, cardiac serious adverse events were reported in 34 individuals, of whom 15 (44%) were aged 65 years or older and 30 (88%) had increased risk or alternate aetiology for cardiac events. These data support the absence of causal relationship.

Tixagevimab–cilgavimab contains three amino acid substitutions (L234F, L235E, P331S) that decrease Fc receptor binding; there is no evidence that it causes platelet activation.[4] Presently, there is no plausible mechanism for cardiac and vascular events given that tixagevimab–cilgavimab does not bind endogenous proteins.

Risk of severe COVID-19 outcomes, including hospitalisation and death in immunocompromised individuals with reduced protective options, persists.[5] Tixagevimab–cilgavimab benefit–risk remains in favour in these vulnerable individuals, and will be continually monitored.

SM, AK, AT, and MTE are employees of, and hold or might hold stock in, AstraZeneca. HM has received consultation fees from AstraZeneca and is supported by the UK National Institute for Health Research's Comprehensive Biomedical Research Centre at University College London Hospitals. HM has consulted for Millfield Medical. on the development of a new continuous positive airway pressure machine. Authors acknowledge Galina Marr, Eva Johnsson, Gavin C K W Koh, and Yee-Man Ching, of AstraZeneca for critical review of the letter. Medical writing support was provided by Rob Campbell, and India Wright of Core Medica, London, UK, supported by AstraZeneca according to Good Publication Practice 2022 guidelines. This analysis was funded by AstraZeneca, and includes data from the PROVENT and STORM CHASER trials that were funded by AstraZeneca and the US Government. AZD7442 is being developed with support from the US Government, including federal funds from the Department of Health and Human Services, Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority in partnership with the Department of Defense, and Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense, under Contract Number W911QY-21-9-0001.

*Sheetal Maselkar, Alexandre Kiazand, Alison Templeton, Hugh Montgomery, *Mark T Esser*
mark.esser@astrazeneca.com

Patient Safety, Chief Medical Office, R&D (SM, AK) and Vaccines and Immune Therapies, BioPharmaceuticals R&D (MTE), AstraZeneca, Gaithersburg, MD 20878-2204, USA; Biometrics, Vaccines and Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK (AT); Department of Medicine, University College London, London, UK (HM)

1 Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. *N Engl J Med* 2022; **386:** 2188–200.
2 Montgomery H, Hobbs FDR, Padilla F, et al. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2022; **10:** 985–996.
3 US Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld™ (tixagevimab co-packaged with cilgavimab). https://www.fda.gov/media/154701/download (accessed June 16, 2022).
4 Loo YM, McTamney PM, Arends RH, et al. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in nonhuman primates and has an extended half-life in humans. *Sci Transl Med* 2022; **14:** eabl8124.
5 Di Fusco M, Lin J, Vaghela S, et al. COVID-19 vaccine effectiveness among immunocompromised populations: a targeted literature review of real-world studies. *Expert Rev Vaccines* 2022; **21:** 435–51.