Journal name: Drug Safety

Challenges and opportunities for signal detection during public health emergencies: an historical reevaluation of the disproportionality analysis of the ADR reporting of anti-COVID-19 monoclonal antibodies in Vigibase

Running heading: **Signal Detection of Anti-COVID-19 mAbs During Public Health Emergencies**

Nicoletta Luxi[#1], Chiara Bellitto[#1], Francesco Ciccimarra[1], Fabio Scapini[1], Elena Arzenton[1], Francesco Maccarrone[1], Ugo Moretti[1], Emanuel Raschi[2], Elisabetta Poluzzi[2], Daniele Focosi[3], Jacopo Angelini[4,5], Pasquale De Nardo[6], Alessia Savoldi[6], Evelina Tacconelli[6], Gianluca Trifirò[1], Marco Tuccori[1*]

1. Department of Diagnostics and Public Health, Section of Pharmacology, University of Verona, Piazzale L.A. Scuro 10, 37134, Verona, Italy.
2. Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy.
3. North-Western Tuscany Blood Bank, Pisa University Hospital, Pisa, Italy.
4. Clinical Pharmacology and Toxicology Institute, University Hospital Friuli Centrale ASUFC, 33100 Udine, Italy.
5. Department of Medicine (DMED), University of Udine (UNIUD), Udine, Italy
6. Infectious Diseases Division, Department of Diagnostics and Public Health, University of Verona, Verona, Italy.

[#]Contributed equally

*Corresponding author

Prof. Marco Tuccori

e-mail: marco.tuccori@univr.it

Address: Piazzale L.A. Scuro, 10, 37134, Verona, Italy

Supplementary Material.

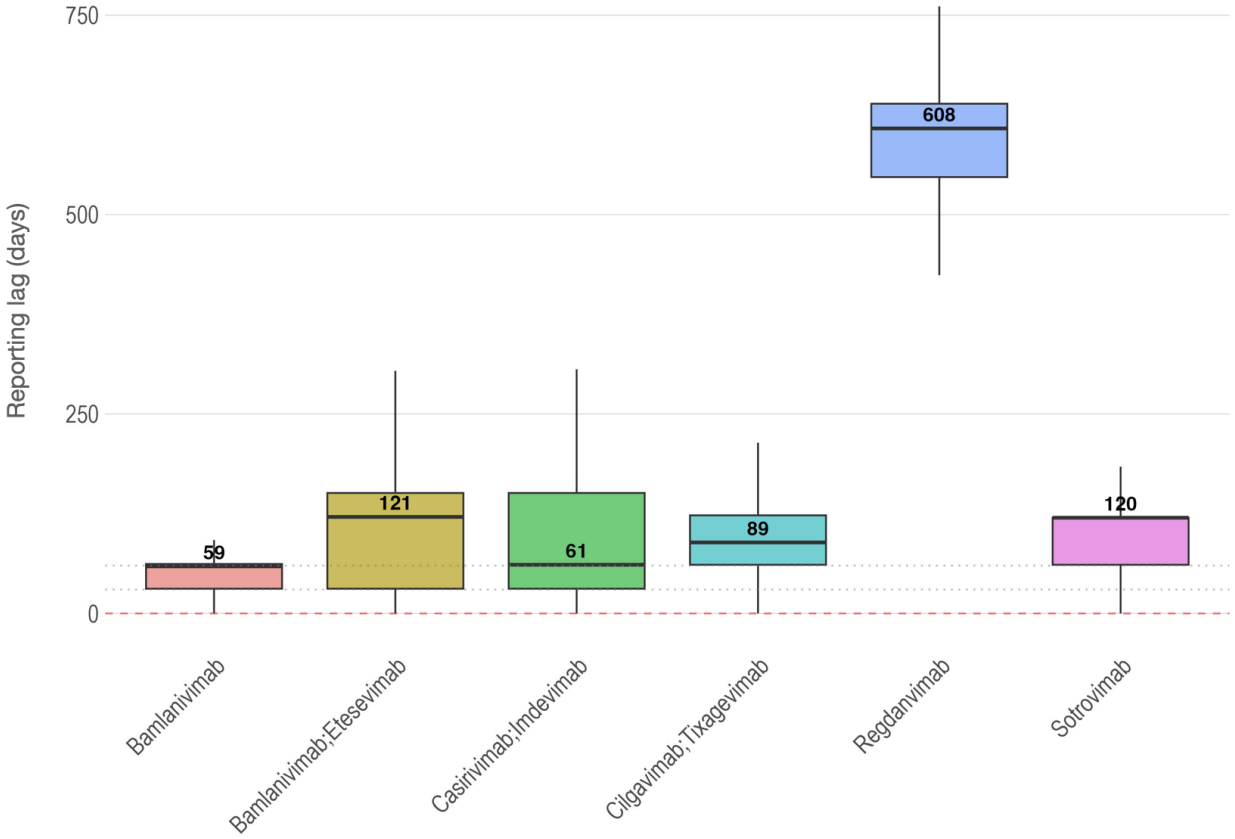
Supplementary Table 1. The READUS-PV checklist.

Section and topic	Item #	Checklist item	Location where item is reported
Title			
	1a	*If disproportionality analyses are a prominent component of the published study, the study should be identified as a "disproportionality analysis". The type of data and name of the database(s) should be specified.*	*Page 1*
	1b	*Report the name of adverse event(s) and/or drug(s) under study, when applicable.*	*Page 1*
Introduction			
Background	*2a*	*Describe the drug(s) and its utilization, the nature of the adverse event(s) under study and its frequency, and the existing knowledge on the drug-event combination.*	*Page 3*
	2b	*Specify the rationale for performing the analysis, e.g., as part of routine pharmacovigilance, to investigate an overall safety profile, or to assess a pre-specified hypothesis.*	*Page 3*
	2c	*Explain why ICSR databases and disproportionality analysis are suitable to fill the knowledge gap.*	*Page 3*
Objectives	*3*	*State specific objectives, identifying the adverse event(s), the drug(s), and the reference group, including any pre-specified hypothesis, if applicable.*	*Page 3*
Methods			
Study design	*4a*	*Identify the study (i.e., "disproportionality analysis") and the type of data used (e.g., "individual case safety reports").*	*Page 3-4*
	4b	*Provide an outline of the entire study design, including primary and sensitivity analyses performed, and other designs such as case-by-case analysis or literature review.*	*Page 4*
Data description, access, and pre-processing	*5a*	*Specify the name of the database(s), the database(s) custodian, and the coverage. Specify the type/number of drugs included within the database and the thesaurus, taxonomies, or ontologies used for coding drugs and events.*	*Page 4*
	5b	*Specify the extraction dates and describe and justify all choices used for data pre-processing, including any data transformation or exclusion, if appropriate.*	*Page 4*
Variables definition	*6a*	*Describe the study population, including any restriction.*	*Page 4*
	6b	*Describe the nature and the meaning of key variables assessed in the work.*	*Page 4*

	6c	*Specify and justify any grouping of drugs or events. For drugs, specify and justify whether active ingredients/trade names/salts were considered and/or the selected role.*	*Page 4*
	6d	*Describe any additional data source used, the type of data, and how they interact with ICSRs.*	*NA*
Statistical methods	*7a*	*Present any descriptive analysis performed, specifying variables investigated, statistical tests, and significance thresholds.*	*Page 4-5*
	7b	*Describe the measure(s) selected for the disproportionality analysis including any threshold used to identify signals of disproportionate reporting. Explain the reason for this choice if applicable.*	*Page 4-5*
	7c	*Clearly describe any sensitivity analysis and any tool to control confounding, including any restriction, subgroup, stratification, adjustment, or interaction.*	*Page 4-5*
	7d	*Specify the variables and methods used for the case-by-case analysis, including any algorithm or criteria used to assess causality, if performed.*	*NA*
	7e	*Specify any statistical methods used for other data sources.*	*NA*
Results			
Participants	*8a*	*Specify the number of individual case safety reports included at each stage, including reasons for exclusion.*	*Page 5*
	8b	*Provide key demographic and clinical characteristics of cases, if possible comparing cases with any appropriate reference group.*	*Page 5*
Disproportionality analysis	*9*	*Present all results including confidence intervals. Present also results of sensitivity analyses, if performed.*	*Page 5-6*
Case-by-case analysis	*10*	*Present the case-by-case analysis of key variables. Present the causality assessment, if applicable.*	*NA*
Discussion			
Key results	*11*	*Discuss key results with reference to study objectives and contextualize them within the current literature and other consulted sources. Clearly discriminate between expected reactions and emerging safety signals.*	*Page 6-8*
External validity	*12a*	*Discuss the external validity of the results to the general population.*	*NA*
	12b	*Discuss the potential relevance of results in clinical practice*	*NA*
	12c	*Propose further study designs if applicable*	*NA*
Limitations	*13*	*Present general limitations, making clear that disproportionality analysis alone cannot prove causation or measure incidence, and specific limitations, including confounding and reporting bias and efforts to mitigate them.*	*Page 8*

Declarations			
	14a	*Provide the source of funding/sponsorship and the role of the funders/sponsors for the present study and for any original study on which the present article is based.*	*Page 9*
	14b	*Clearly identify potential commercial and intellectual conflicts of interest (e.g., link to any drug/event investigated, whether financial, legal action, or software used).*	*Page 9*
	14c	*Declare any institutional approval needed or granted in the investigation.*	*Page 9*
	14d	*Include a statement on data availability, code availability (including the version of the statistical software used), and protocol registration.*	*Page 9*

Supplementary figure 1. Distribution of reporting lag, expressed in days and defined as the difference between the date the report was received in VigiBase and the date of event onset as recorded in the ICSR.



Legend=Boxplot represent the median and interquartile range in days

Supplementary Table 2. Timeline of regulatory approvals and withdrawals fo study drugs across EMA and FDA.

	EMA		**FDA**	
	Date of authorization	**Withdrawal**	**Date of authorization**	**Withdrawal**
Bamlanivimab	-	-	09/11/2020	15/04/2021
Bamlanivimab/etesevimab	11/03/2021	29/10/2021	09/02/2021	24/01/2022 (restricted)
Casirivimab/imdevimab	12/11/2021	-	21/11/2020	24/01/2022 (restricted)
Regdanvimab	12/11/2021	-	-	-
Sotrovimab	17/12/2021	-	26/05/2021	05/04/2022
Tixagevimab/cilgavimab	15/09/2022	-	-	-
Legend= EMA: European Medicines Agency; FDA: Food and Drug Administration				

Supplementary Table 3. The selection process of drug-adverse reaction pairs for the disproportionality analysis.

Step	Exclusion criteria	Overall N (%)	Bamlanivimab	Bamlanivimab/etesevimab	Casirivimab/imbevimab	Tixagevimab/cilgavimab:	Regdanvimab	Sotrovimab
0	-	**42,799 (100)**	**11,903**	**6,313**	**16,251**	**3,255**	**823**	**4,254**
1	Removing PTs included in SOC “Respiratory, thoracic and mediastinal disorders”, “Infection and infestations”, “Product issues”, “Surgical and medical procedures”, “Injury, poisoning, and procedural complications”	**34,583 (80.8)**	9,155 (76.9)	5,060 (80.1)	13,332 (82.1)	2,615 (80.3)	803 (97.6)	3,618 (85.0)
2	Removing the following PTs: "Oxygen saturation decrease", “Condition aggravated”, “Disease complication”, “Disease occurrences”, “Disease progression”, “Therapeutic response unexpected”.	**34,305 (80.2)**	9,064 (76.1)	5,036 (79.8)	13,235 (81.4)	2,599 (79.8)	801 (97.3)	3,570 (83.9)
3	Removing PTs included in the SMQ “COVID-19”	**34,249 (80.0)**	9,054 (76.1)	5,033 (79.7)	13,220 (81.3)	2,588 (79.5)	801 (97.3)	3,553 (83.5)
4	Removing PT included in the SMQ “Lack of efficacy”	**33,948 (79.3)**	9,002 (75.6)	5,006 (79.3)	13,130 (80.8)	2,527 (77.6)	801 (97.3)	3,482 (81.9)
5	Removing PTs non-IME	**3,047 (7.1)**	869 (7.3)	324 (5.1)	1,135 (7.0)	392 (12.0)	47 (5.7)	280 (6.6)
6	Removing drug-PT pairs with non-significant ROR values	**1,676 * (3.9)**	472 (4.0)	183 (2.9)	689 (4.2)	189 (5.8)	38 (4.6)	105 (2.5)

*Legend=*83 unique drug-reaction pairs;*
SOC=System Organ Class; PT=Preferred Term; SMQ=Standardised MedDRA Queires; IME= Important Medical Events; ROR=Reporting Odds Ratio

Supplementary Table 4. Notoriety assessment of ADRs at MedDRA PT level with a statistically significant ROR for the study drugs.

					Notoriety		
bamlanivimab							
MedDRA SOC	**MedDRA PT**	**N**	**ROR (95% CIs)**	**AESI Brighton collaboration**	**FDA**	**EMA**	**Linked***
General disorders and administration site conditions	Systemic inflammatory response syndrome	5	27.69 (11.5-66.9)			-	
Cardiac disorders	Acute myocardial infarction	23	18.5 (12.3-27.9)			-	
Nervous system disorders	Unresponsive to stimuli	28	17.74 (12.2-25.8)			-	
Cardiac disorders	Myocardial ischaemia	5	13.11 (5.4-31.6)			-	
Nervous system disorders	Encephalopathy	18	9.6 (6-15.3)	X		-	
Cardiac disorders	Atrial fibrillation	74	8.66 (6.9-10.9)		X	-	
Nervous system disorders	Facial paralysis	7	7.54 (3.6-15.9)	X		-	
Cardiac disorders	Bradycardia	48	6.43 (4.8-8.6)		X	-	
Cardiac disorders	Cardio-respiratory arrest	12	5.58 (3.2-9.9)			-	
Cardiac disorders	Ventricular tachycardia	5	5.25 (2.2-12.6)			-	Tachycardia
Nervous system disorders	Syncope	49	5.06 (3.8-6.7)			-	
Metabolism and nutrition disorders	Diabetic ketoacidosis	9	4.64 (2.4-8.9)			-	
Gastrointestinal disorders	Pancreatitis acute	8	4.52 (2.3-9.1)			-	
Vascular disorders	Deep vein thrombosis	16	4.45 (2.7-7.3)			-	
Cardiac disorders	Myocarditis	5	4.11 (1.7-9.9)			-	
Renal and urinary disorders	Acute kidney injury	57	4.07 (3.1-5.3)			-	

Psychiatric disorders	Delirium	12	3.47 (2-6.1)			-	
Nervous system disorders	Transient ischaemic attack	6	3.2 (1.4-7.1)			-	
Cardiac disorders	Cardiac arrest	17	2.96 (1.8-4.8)			-	
Nervous system disorders	Depressed level of consciousness	9	2.65 (1.4-5.1)			-	
Nervous system disorders	Loss of consciousness	26	2.56 (1.7-3.8)			-	
Investigations	Electrocardiogram QT prolonged	8	2.29 (1.1-4.6)			-	
Nervous system disorders	Cerebrovascular accident	25	2.08 (1.4-3.1)			-	
bamlanivimab/etesevimab							
MedDRA SOC	**MedDRA PT**	**N**	**ROR (95% CIs)**	**AESI Brighton collaboration**	**FDA**	**EMA**	**Linked***
Nervous system disorders	Unresponsive to stimuli	19	23.59 (15-37.1)			-	
Nervous system disorders	Syncope	31	6.29 (4.4-9)		X	-	
Metabolism and nutrition disorders	Diabetic ketoacidosis	7	7.08 (3.4-14.9)			-	
Cardiac disorders	Angina pectoris	6	6.37 (2.9-14.2)			-	
Cardiac disorders	Cardio-respiratory arrest	6	5.46 (2.5-12.2)			-	
Cardiac disorders	Bradycardia	17	4.44 (2.8-7.2)		X	-	
Cardiac disorders	Atrial fibrillation	15	3.39 (2-5.6)		X	-	
Immune system disorders	Anaphylactic reaction	36	2.97 (2.1-4.1)	X	X	-	
Nervous system disorders	Loss of consciousness	15	2.89 (1.7-4.8)			-	Altered mental status Vasovagal reactions
Vascular disorders	Deep vein thrombosis	5	2.72 (1.1-6.5)			-	
Renal and urinary disorders	Acute kidney injury	16	2.22 (1.4-3.6)			-	
Metabolism and nutrition disorders	Hypokalaemia	10	1.95 (1-3.6)			-	

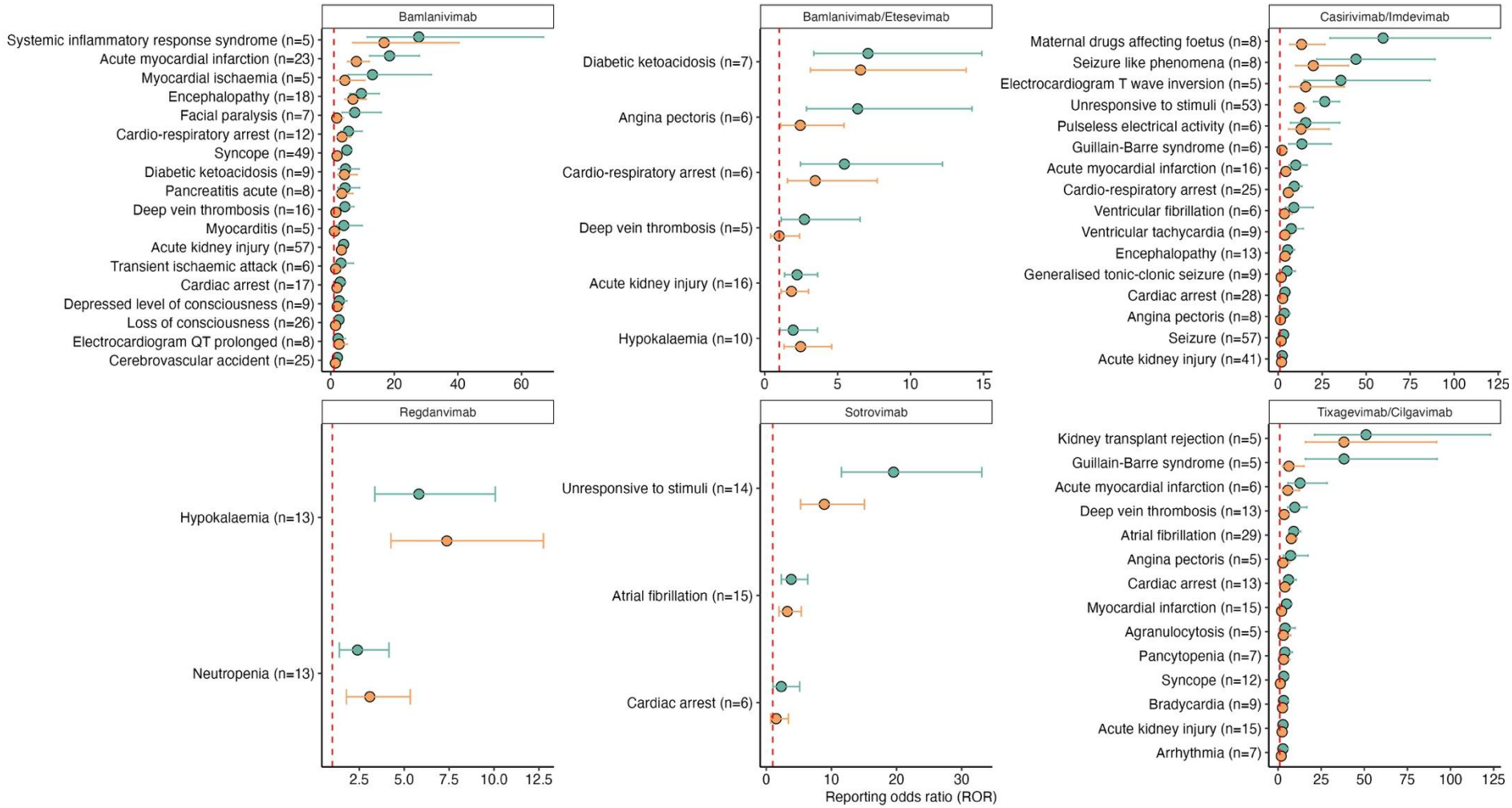
casirivimab/imdevimab							
MedDRA SOC	**MedDRA PT**	**N**	**ROR (95% CIs)**	**AESI Brighton collaboration**	**FDA**	**EMA**	**Linked***
Injury, poisoning and procedural complications	Maternal drugs affecting foetus	8	59.6 (29.5-120.6)				
Nervous system disorders	Seizure like phenomena	8	44.15 (21.9-89.1)	X			
Investigations	Electrocardiogram T wave inversion	5	35.6 (14.7-86.3)				
Nervous system disorders	Loss of consciousness	79	6.13 (4.9-7.7)				Altered mental status Vasovagal reactions
Cardiac disorders	Bradycardia	60	6.27 (4.9-8.1)		X		
Nervous system disorders	Unresponsive to stimuli	53	26.45 (20.1-34.7)				
Cardiac disorders	Pulseless electrical activity	6	15.61 (7-34.9)				
Renal and urinary disorders	Acute kidney injury	41	2.27 (1.7-3.1)				
Nervous system disorders	Guillain-Barre syndrome	6	13.44 (6-30)	X			
Cardiac disorders	Acute myocardial infarction	16	9.98 (6.1-16.3)				
Cardiac disorders	Cardio-respiratory arrest	25	9.11 (6.1-13.5)				
Cardiac disorders	Ventricular fibrillation	6	8.9 (4-19.9)				
Nervous system disorders	Syncope	107	8.71 (7.2-10.6)		X	X (convulsive syncope)	
Cardiac disorders	Ventricular tachycardia	9	7.38 (3.8-14.2)				
Nervous system disorders	Encephalopathy	13	5.39 (3.1-9.3)	X			
Nervous system disorders	Generalised tonic-clonic seizure	9	5.02 (2.6-9.7)	X			
Cardiac disorders	Cardiac arrest	28	3.81 (2.6-5.5)				
Immune system disorders	Anaphylactic reaction	107	3.53 (2.9-4.3)	X	X	X	
Cardiac disorders	Atrial fibrillation	38	3.42 (2.5-4.7)		X		

Cardiac disorders	Angina pectoris	8	3.38 (1.7-6.8)				
Nervous system disorders	Seizure	57	3.06 (2.4-4)	X			
tixagevimab/cilgavimab							
MedDRA SOC	**MedDRA PT**	**N**	**ROR (95% CIs)**	**AESI Brighton collaboration**	**FDA**	**EMA**	**Linked***
Immune system disorders	Kidney transplant rejection	5	51.02 (21.1-123.2)				
Nervous system disorders	Guillain-Barre syndrome	5	38.25 (15.9-92.3)	X			
Cardiac disorders	Acute myocardial infarction	6	12.74 (5.7-28.4)				
Vascular disorders	Deep vein thrombosis	13	9.67 (5.6-16.7)				
Cardiac disorders	Atrial fibrillation	29	9.01 (6.2-13)				
Nervous system disorders	Unresponsive to stimuli	5	8.35 (3.5-20.1)		X		
Cardiac disorders	Angina pectoris	5	7.21 (3-17.4)				
Cardiac disorders	Cardiac arrest	13	6.04 (3.5-10.4)				
Cardiac disorders	Myocardial infarction	15	4.88 (2.9-8.1)				
Blood and lymphatic system disorders	Agranulocytosis	5	4.07 (1.7-9.8)				
Blood and lymphatic system disorders	Pancytopenia	7	3.91 (1.9-8.2)				
Nervous system disorders	Syncope	12	3.28 (1.9-5.8)				
Immune system disorders	Anaphylactic reaction	29	3.25 (2.3-4.7)	X	X	X	
Cardiac disorders	Bradycardia	9	3.18 (1.7-6.1)				
Renal and urinary disorders	Acute kidney injury	15	2.83 (1.7-4.7)				
Cardiac disorders	Arrhythmia	7	2.8 (1.3-5.9)				

Nervous system disorders	Loss of consciousness	9	2.35 (1.2-4.5)		X		vaso-vagal reactions (e.g., pre-syncope, syncope)
Regdanvimab							
MedDRA SOC	**MedDRA PT**	**N**	**ROR (95% CIs)**	**AESI Brighton collaboration**	**FDA**	**EMA**	**Linked***
Cardiac disorders	Bradycardia	12	7.18 (4.1-12.7)		-	X	
Metabolism and nutrition disorders	Hypokalaemia	13	5.82 (3.4-10.1)		-		
Blood and lymphatic system disorders	Neutropenia	13	2.4 (1.4-4.2)		-		
Sotrovimab							
MedDRA SOC	**MedDRA PT**	**N**	**ROR (95% CIs)**	**AESI Brighton collaboration**	**FDA**	**EMA**	**Linked***
Nervous system disorders	Unresponsive to stimuli	14	19.54 (11.5-33.1)				
Cardiac disorders	Bradycardia	25	7.41 (5-11)		X	X	
Nervous system disorders	Syncope	18	4.09 (2.6-6.5)		X		
Psychiatric disorders	Delirium	6	3.84 (1.7-8.6)		X	X	
Cardiac disorders	Atrial fibrillation	15	3.83 (2.3-6.4)				
Cardiac disorders	Cardiac arrest	6	2.3 (1.1-5.1)				
Immune system disorders	Anaphylactic reaction	21	1.94 (1.3-3)	X		X	

** Linked: adverse event judged to be reported in the product label using a related, non-identical term.*
N= number of report; MedDRA= Medical Dictionary for Regulatory Activities; SOC = System Organ Class; PT = Preferred Term

Supplementary Figure 2. Forest plot of disproportionality analysis (main analysis vs. sensitivity analysis) of unlabeled ADRs (at PT MedDRA level), stratified by single drug.



Legend: For each ADR, the two distinct colored points with horizontal error bars compare the estimates from the main analysis (green) against the sensitivity analysis (orange).