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Supplementary appendix

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Table S1. Characteristics of TTS cases after the second dose of AZD1222

Region	Age group, yrs / sex	Symptom onset, days post second dose	Site of thrombosis	Bleeding or coagulopathy	Platelet nadir, 10^9/L	Other medical conditions	Concomitant medications	Other laboratory findings	Treatment	Outcome	Comment
EU/EEA	45–60 / M	7	Pulmonary embolism Pelvic venous thrombosis	Pulmonary hemorrhage INR increased Pericardial effusion Pleural effusion	127	Unk	Unk	Anti-PF4 antibodies: Unk Coags: INR=1·38	Unk	Recovering	
UK	61–85 / M	3	Pulmonary embolism Cardiac disorder (right heart strain)	None	119	Papillary cystadenoma lymphomatosum Benign prostatic hyperplasia Myocarditis Diverticulum Squamous cell carcinoma of skin (Bowen's disease) Dementia Alzheimer's type Cholelithiasis Pleural fibrosis Psoriasis Vitamin B12 deficiency GERD	Leuprorelin	Anti-PF4 antibodies: Negative (0·026; cut-off 0·150) Coags: APTT: 37·0 (ratio 1·2) D-dimers: >20,000 Blood fibrinogen: 2·6 PT: 13·3	Argatroban infusion; IVIg, apixaban	Recovering	Prostate-specific antigen was found to be significantly raised; negative COVID-19 test
UK	45–60 / F	10	CVST Pulmonary embolism	None	Unk	Hypertension	Unk	Anti-PF4 antibodies: Unk Coags: Unk	Unk	Not recovered	Limited information
UK	45–60 / F	8	Pulmonary embolism	None	113	DVT Suspected COVID-19	Unk	Anti-PF4 antibodies: Negative (value not available) Coags: D-dimers: 929	Unk	Recovering	Positive COVID-19 test
UK	61–85 / F	9	Pulmonary embolism Embolism Angina pectoris	None	Unk	Angina pectoris Hypertension Hypercholesterolemia Diverticulum Asthma Atrioventricular block	Unk	Anti-PF4 antibodies: Unk Coags: Unk	Unk	Fatal	Pulmonary embolism was a post-mortem findings

						Type 2 diabetes mellitus Pacemaker Cervical spondylosis					
UK	61-85 / F	13	Pulmonary embolism	Hemorrhage intracranial Subarachnoid hemorrhage	103	Hysterectomy Hypertension Non-alcoholic fatty liver disease	Unk	Anti-PF4 antibodies: Unk Coags: APTT: 65·4 Fibrinogen: 0·6 PT:17	Unk	Fatal	
UK	Unk / M	1	CVST	Purpura non-thrombocytopenic	58	Myocardial ischemia Prostate cancer Cardiac failure Neurodermatitis	Unk	Coags: Unk	As hemoglobin was also low, he was transfused	Not recovered	Conflicting information regarding both purpura and radiographic findings excluding cavernous venous thrombosis
UK	61–85 / M	11	DVT	Cerebral hemorrhage	93	Prostate cancer with recent diagnosis of bone metastasis COPD Myocardial ischemia Cardiac assistance device user Cerebrovascular accident Atrial fibrillation	Bicalutamide	Anti-PF4 antibodies: Negative (ELISA; value not available) Coags: APTT: 38 Fibrinogen: 1.1 D-dimers: 20000 PT: 31	Anticoagulation / antiplatelet medication at admission; one dose of IVIg	Fatal	The vaccinee had arm swelling and the patient was due to have an ultrasound doppler of his arm to determine if it was a DVT or cellulitis. He also had confusion and CT head with contrast showed the multiple spontaneous bleeds. The cause of death was cerebral hemorrhage
UK	61–85 / M	5	Embolism Pulmonary embolism	Hemorrhage	117	Emphysema Head injury Fall Thrombocytopenia Aortic aneurysm Vena cava filter insertion	Anti-d immunoglobulin	Anti-PF4 antibodies: Unk Coags: APTT: 30·5 Fibrinogen: 0·9 D-dimers: 83·82 µg/ml FEU PT:13·6	Unk	Recovered with sequelae	Platelet count in November 2020 was 145 and concomitant Anti-d immunoglobulin. Past drug heparin
UK	61–85 / F	3	Thrombotic stroke	None	Unk	Unk	Ramipril	Anti-PF4 antibodies: Unk Coags: Unk	Unk	Not recovered	Limited information
UK	61–85 / F	3	Embolism	Contusion Epistaxis	5	Diabetes mellitus Pulmonary embolism DVT	Amlodipine for hypertension, atorvastatin for high cholesterol and latanoprost for glaucoma. Past drug therapy	Anti-PF4 antibodies: Unk Coags: APTT: 1·09 Fibrinogen: 4·16 PT: 1·0		Not recovered	Platelet count in March 2021 was 209

							included heparin				
UK	61–85 / F	<10	Cerebrovascular accident Embolism	None	<150	Atrial fibrillation	Apixaban, bisoprolol, digoxin for atrial fibrillation, furosemide for oedema, memantine for memory loss	Anti-PF4 antibodies: Unk Coags: Unk	Unk	Not recovered	Limited information. Past drugs included heparin
UK	45–60 / F	5	CVST Pulmonary embolism	None	27	Bilateral lung metastases, brain mets hilar and mediastinal lymph nodes, grade 3 Radiotherapy Breast cancer (grade 3; ER6; PR4; HER2 negative) Head injury	Capecitabine, letrozolefor breast cancer (since April 16, 2021), enoxaparin for prophylaxis (from April 16–29, 2021)	Anti-PF4 antibodies: Unk Coags: APTT: 23 Fibrinogen:4·6 D-dimers: 4898 PT: 12	Non-heparin anticoagulation; antiplatelet medication	Not recovered	Patient was started on capecitabine, letrozole for breast cancer, and enoxaparin for prophylaxis 8 days before dose 2: last radiotherapy treatment 18 days before dose 2. Past drugs included heparin

Due to the incompleteness of post-market reporting, some information is unknown. This is denoted in the table. Other unknown information at the time of data cutoff includes the time from the second dose to the start of platelet count drop, and to platelet nadir. To protect patient privacy, patient region is reported as either EU/EEA or UK, and ages are reported in two categories: 45–60 yrs or 61–85 yrs.

APTT, activated partial thromboplastin time; Coags, coagulation profile; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; CT, computerized tomography; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; ER6, estrogen receptor 6; F, female; European Economic Area, EEA; European Union, EU; GERD, gastroesophageal reflux disease; HER2, human epidermal growth factor receptor 2; INR, international normalized ratio; IVIg, intravenous immunoglobulin; M, male; PF4, platelet factor 4; PR4, progesterone receptor 4; PT, prothrombin time; TTS, thrombosis with thrombocytopenia; yrs, years; Unk, unknown.

Table S2. Estimated Background TTS Rates Using Two Analysis Methods with the US Truven MarketScan Commercial Claims and Encounters database from January 1, 2019 to December 31, 2019

	Event rate using method 1*	Event rate using method 2†
Event rate per 1 million persons per 14-days (95% CI)	3·75 (3·51–4·00)	7·16 (6·83–7·51)

Analysis was restricted to first TTS events enrollees aged 18 years or older on Jan 01, 2019. Rates (95% CI) were calculated by dividing the number of observed events with the person-time at risk (calculated from either the date of study period start to date of event; time of censoring due to end of continuous enrollment; or end of follow-up period). Standardization provided the rate per one million persons per 14 days. *Defined as primary or unspecified thrombocytopenia occurring between seven days before and seven days after thrombosis event (focused on thrombosis of limbs, splanchnic region, and cerebral or pulmonary embolism) limited to patients without a history of thrombocytopenia and/or thrombotic event 12 months prior. †Defined as primary or unspecified thrombocytopenia occurring the day before, or 14 days after, thrombosis. CI, confidence interval; TTS, thrombosis with thrombocytopenia syndrome.

Contributors

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