

## Very rare thrombosis with thrombocytopenia after second AZD1222 dose: a global safety database analysis

Since COVID-19 vaccine roll-out, very rare cases of thrombosis with thrombocytopenia syndrome (TTS), which has been referred to as vaccine-induced immune thrombotic thrombocytopenia, have been reported. Here we describe case details of TTS identified in the AstraZeneca global safety database, which captures all spontaneously reported adverse events from real-world use of its medicines and vaccines worldwide.

All cases of TTS occurring within 14 days of intramuscular administration of first or second AZD1222 (ChAdOx nCoV-19) dose up to April 30, 2021, were included. In alignment with the Brighton Collaboration definition of TTS,<sup>1</sup> TTS cases were searched using standardised Medical Dictionary for Regulatory Activities (version 23.1) queries "embolic and thrombotic events", "hematopoietic thrombocytopenia", and high-level term "thrombocytopenias". The understanding of the role of anti-platelet factor 4 (PF4) antibodies in TTS is still evolving, so in line with the Brighton criteria, all cases meeting the above definition, irrespective of anti-PF4 antibodies, were included. This research was led and funded by AstraZeneca.

At data cutoff, 13 cases of TTS were identified after the second AZD1222 dose, occurring 1–13 days post-vaccination (appendix p 1; no cases were observed outside the 14-day window). The reported events included eight individuals with pulmonary embolism, co-occurring with cerebral venous sinus thrombosis (CVST) in two individuals; one individual with CVST occurring alone; one individual with deep vein thrombosis;

one individual with thrombotic stroke; and two individuals with unspecified embolisms. The 13 vaccinees reporting TTS were aged 45–85 years (one age unknown); eight were female (a lower proportion than in initial TTS reports<sup>2</sup>). Medical history was available for 11 vaccinees; one had previous pulmonary embolism, one had thrombocytopenia, three had cancer, and one had COVID-19. Other medication details were available for seven vaccinees and included cancer treatments, antihypertensives, anticoagulants, and statins. Anti-PF4 test results were available for three of 13 cases, all of which were negative (appendix p 1). At data cutoff, six vaccinees were reported as "not recovered", three were "recovering", three died, and one "recovered with sequelae".

Based on weekly data from the European Centre for Disease Prevention and Control and the UK Department of Business Energy and Industrial Strategy, as of April 25, 2021, approximately 5.62 million people were estimated to have received the second AZD1222 dose in the EU/EEA and in the UK (93.5% administered in the UK). Based on this exposure level, the estimated rate of TTS within 14 days of the second AZD1222 dose was 2.3 per million vaccinees.

By comparison, within the same timeframes, the estimated rate of TTS within 14 days of the first dose was 8.1 per million vaccinees, based on 399 cases of TTS identified after the first AZD1222 dose and approximately 49.23 million first doses administered, with 45.2% of doses administered in the UK and 54.8% in the EU/EEA.

We estimated background TTS rates using two analysis methods with the US Truven MarketScan Commercial Claims and Encounters database from Jan 1, 2019, to Dec 31, 2019. The very low rate of TTS reported following a second AZD1222 dose is within preliminary estimates of the background range in an unvaccinated

population pre-COVID-19 (appendix p 4).<sup>3</sup>

Limitations of this safety database analysis include a reliance on health-care provider-reported and vaccinee-reported data, which might result in event under-reporting. Furthermore, heightened media attention might have led to event misclassification. Therefore, to provide a cautious estimate for the event rate, data used for the number of doses administered was limited to the EU/EEA and the UK, while all cases reported globally were included.

As common in post-market reporting, limited information was provided in many cases, including medical history and concomitant medication. Additionally, comparing incidence rates, including background rates, can be challenging due to dependence on data sources, event definitions, data collection method, timeframe, and the patient population. The TTS background event rate reported here was derived from a large US population with health insurance in 2019, prior to the emergence of COVID-19, a disease which itself has been associated with thrombotic events.<sup>4</sup>

Although post-marketing surveillance reporting does not enable full characterisation and contextualisation of each case, overall results support the continued administration of AZD1222 in a two-dose schedule, as indicated.<sup>5</sup> This is particularly relevant in light of recent data demonstrating the efficacy of two doses of AZD1222 against SARS-CoV-2 variants of concern, including protection against hospitalisation with the Delta variant.<sup>6,7</sup>

We are employees of AstraZeneca and might have stock or options, or both. Details of contributions are shown in the appendix.

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Published Online  
July 27, 2021  
[https://doi.org/10.1016/S0140-6736\(21\)01693-7](https://doi.org/10.1016/S0140-6736(21)01693-7)

See Online for appendix

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