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PLATO Controversy Hits the *Wall Street Journal*

Michael O'Riordan | February 05, 2014

NEW YORK, NY – The controversy surrounding the **PLATO** trial of **ticagrelor** (Brilinta, AstraZeneca) continues unabated, according to a story published in the *Wall Street Journal*. Specifically, a sealed complaint filed in US district court in the District of Columbia by a researcher contends that the cardiovascular events in the study "may have been manipulated" [1].

Dr Victor Serebruany (HeartDrug Research Laboratories, Johns Hopkins University, Towson, MD), who has long been a thorn in the side of AstraZeneca and the PLATO investigators, filed the complaint under the **False Claims Act**, reports the *Wall Street Journal*. The *Journal* notes that the US attorney's office in Washington, DC, has contacted Serebruany and is currently investigating the clinical trial. As reported by **heart *wire*** in October 2013, the US **Department of Justice** issued a civil investigative demand from its civil division "seeking documents and information regarding PLATO." AstraZeneca is complying with the request.

First reported by **heart *wire*** in 2009 , the PLATO trial was a positive study involving more 18 000 patients from 43 countries. PLATO investigators, led by **Dr Lars Wallentin** (Uppsala Clinical Research Center, Sweden), showed that treating acute coronary syndrome patients with ticagrelor significantly reduced the rate of MI, stroke, and cardiovascular death compared with patients taking **clopidogrel**. Results were presented at the **European Society of Cardiology 2009 Congress** and reported in the *New England Journal of Medicine*.

PLATO has been dogged by questions, including prior to approval. In the sealed complaint, Serebruany takes issue with a number of things, many of which have been reported previously. He alleges that the number of clinical events among those taking clopidogrel was high compared with other studies, pointing out that the rate of all-cause death was 5.9% among clopidogrel-treated patients—nearly twice as high as earlier studies.

In addition, the sealed complaint documents the geographic discrepancies in the trial, noting there was a trend toward worse outcomes with ticagrelor at North American sites. The complaint also alleges that an initial count of clinical events suggested the two drugs were equivalent, but adjudication by the **Duke Clinical Research Institute** attributed another 45 MIs to the clopidogrel group, which tipped the results in favor of ticagrelor. Other questions raised about the study include site monitoring and timing of clinical events. Serebruany also alleges that the trial may have unintentionally been unblinded because of the shape of clopidogrel's "split capsules," which would have enabled doctors and nurses to know which drug patients received.

AstraZeneca rebutted these issues, telling the *Journal* that it is cooperating with the government. It said it is confident in the integrity of the trial and noted the overall study showed the superiority of ticagrelor over clopidogrel. There is no evidence the trial was unblinded and researchers used the same standards when qualifying all clinical events, including MIs, they noted. In addition, the company said it is not possible to compare event rates with clopidogrel in PLATO with other studies because the patient populations differ.

The *Journal* reports that Serebruany became embroiled in the controversy when asked by the **FDA**'s **Dr Thomas Marciniak** to advise the agency about the PLATO data in 2010. Marciniak, who led the FDA's review of PLATO, called AstraZeneca's submission on serious adverse events the "worst submission" he ever encountered. According to the submission, he noted, 12 patients reported their own deaths by telephone. Before approving ticagrelor, the FDA requested an additional analysis of PLATO, and it was eventually approved in the US in July 2011. Ticagrelor was approved in Europe in December 2010 and is authorized for use in more than 100 countries.

The *Journal* called Serebruany an expert in the antiplatelet field but said he is a "controversial figure," partly because of his financial ties to industry and repeated criticisms of new drug approvals. Through HeartDrug Research, Serebruany has worked on **prasugrel** (Effient, Lily/Daiichi-Sankyo), a competing antiplatelet agent, but has also done work for AstraZeneca.

References

1. Burton TM. Doctor challenges testing of AstraZeneca's Brilinta. *Wall Street Journal*, February 2, 2014. Available here.

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