



MEMORANDUM

**FDA places clinical hold on IND for Zafgen's MetAP2 inhibitor ZGN-1061 -
November 27, 2018**

Cites CV risk with predecessor beloranib; Ex-US phase 2 trial to continue as planned, report early 2019; No safety signals reported to date

Zafgen [announced](#) yesterday that FDA has placed a clinical hold on the company's Investigational New Drug (IND) Application for injectable MetAP2 inhibitor ZGN-1061 for type 2 diabetes. According to the [press release](#), FDA cited possible CV risk based on Zafgen's prior MetAP2 inhibitor, beloranib, which was [discontinued](#) in [2Q16](#) due to two thrombosis-related deaths with beloranib in a phase 3 trial. FDA has reportedly outlined both nonclinical and clinical options for moving ZGN-1061 forward, and Zafgen will request a "[Type A](#)" meeting with regulators to discuss next steps - a strategy very similar to that [undertaken for beloranib](#) following its clinical trial hold.

Since beloranib's discontinuation, Zafgen has been working diligently to differentiate ZGN-1061 from its predecessor. An [ex-US phase 1b study](#) for ZGN-1061 [demonstrated](#) a reassuring safety profile, following [preclinical studies](#) that found an [improved safety margin](#) vs. beloranib (with few specifics). Most notably, Zafgen's 12-week [phase 2](#) study of ZGN-1061 outside the US was recently [expanded](#) to include a higher dose based on the [absence](#) of safety signals (including in thrombosis biomarkers) with 0.05, 0.3, and 0.9 mg doses. This study will continue as planned, and topline results are expected in early 2019.

We're eager for more details on this surely complicated decision from FDA. Given that ZGN-1061 comes from a novel class with a complicated safety history, we certainly understand the agency's caution. That said, we also find the absence of safety signals associated with ZGN-1061 to date promising for the candidate's future. Indeed, the great Dr. James Gavin expressed his excitement over ZGN-1061 at TCOYD/The diaTribe Foundation's [12th Annual Diabetes Forum](#) during ADA 2018: "[ZGN-1061] is absolutely wonderful in terms of mechanism of action. It can actually reduce weight and glycemia in type 2 diabetes, as it also reduces hepatic liver scores in NAFLD, so this is a wonderful technology that combines well with other things and could be a whole new class."

--by Peter Rentzepis, Ann Carracher, and Kelly Close