CLOSER LOOK

MEMORANDUM

Zafgen terminates development of Beloranib - July 21, 2016

Executive Highlights

- Based on safety concerns surrounding thrombosis, Zafgen is terminating development of the MetAP2 inhibitor beloranib, a therapy for Prader-Willi Syndrome (PWS) and the most advanced drug in the company's pipeline.
- Zafgan has restructured its resources around the development of ZGN-1061, a MetAP2 inhibitor slated to enter phase 1 clinical trials in 2017.

Today, Zafgen announced that it is terminating development of the methionine aminopeptidase-2 (MetAP2) inhibitor beloranib, which would have been the first available treatment for people with Prader-Willi Syndrome (PWS) and heretofore the most advanced drug in the company's pipeline. This decision follows a complete clinical hold placed on the beloranib Investigational New Drug (IND) application by the FDA last December following the thrombosis-related deaths of two beloranib-treated subjects in a phase 3 clinical trial. In response to the clinical hold, Zafgen held a Type A meeting with the FDA, citing beloranib's impressive efficacy in the treatment of both PWS and severe obesity complicated by type 2 diabetes, proposing a risk evaluation mitigation strategy (REMS) which would involve prophylaxis with anticoagulants, and a proposed phase 3 clinical trial in PWS designed to confirm efficacy and to validate the REMS. After much discussion, Zafgen concluded that the costs timelines, and other obstacles required to obtain FDA marketing approval for beloranib were simply too high to justify - an unfortunate testament to the difficulty of drug development in the obesity arena, especially as it relates to PWS. While we are disappointed to see the termination of the beloranib program, this does not come as a complete surprise as the risk of thrombosis did not outweigh the observed benefits. We will have more information after speaking to the company.

Despite this setback, Zafgen moves ahead in its pursuit of therapies for obesity and metabolic disorders, and will now focus efforts to advance a preclinical second-generation MetAP2 inhibitor in its pipeline: ZGN-1061. Patients are currently being screened to enter a phase 1 trial for the use of ZGN-1061 in the treatment of severe obesity complicated by type 2 diabetes; results are expected by in the first quarter of 2017.

- **In a webcast update call that followed Zafgen's announcement, CEO Tom Hughes shared that he is "disappointed about beloranib, but encouraged by ZGN-1061,"** the product profile of which may avoid the safety limitations of beloranib, while maintaining similar efficacy and potency in the treatment of obesity (as demonstrated in animal models). We are hopeful that if phase 1 data are positive for the treatment of obesity, ZGN-1061 will have potential to reach a wider population people with obesity than would have been seen with beloranib. We certainly hope that ZGN-1061 and the MetAP2 inhibitor class can one day provide another treatment option for the increasing number of people suffering from obesity.
- **ZGN-1061 has a similar efficacy and potency profile as beloranib, but with improved safety margins.** In preclinical trials, ZGN-1061 increased HDL cholesterol and decreased body weight, A1c, triglycerides, blood pressure, and liver fat.
- **Zafgen expressed optimism about its strong cash position to fund the continued development of ZGN-1061 through phase 2a clinical trials.** The company's $150 million in cash and cash equivalent is expected to drive ZGN-1061 through phase 2a clinical trials and fund operations through the end of 2018. It's terrific that they got so much funding when they did. We admire their brainpower and optimism.

- **Ensuring adequate funding for ZGN-1061 required the tough decision to reduce Zafgen's workforce.** The company's workforce will be reduced by 34% to a total of 31 employees by the end of the year.

Close Concerns Questions:

Q: How is the Prader-Willi Syndrome community responding to the news about beloranib's suspension?

Q: How will future clinical trial designs for MetAP2 inhibitors address the potential risk of thrombosis with this drug class?

Q: Does Zafgen plan to pursue a general obesity indication for ZGN-1061, or something more specific? Given the preclinical data which suggest a positive effect of ZGN-1061 on liver fat, is there potential for an indication for NASH/NAFLD?

Q: Will interest in beloranib be renewed? Are there feasible solutions to overcome its safety hazards?

-- by Abigail Dove, Sarah Odeh, and Kelly Close