

## The end of another chapter in obesity drug development



[Jacob Plieth](#)

The development of drugs to treat obesity has been through several highs and lows over the past 25 years, and with Zafgen ditching beloranib yesterday the sun looks to have set on the latest iteration of the cycle.

A reaction even starker than Zafgen stock crashing 50% this morning came from RBC Capital Markets' Simos Simeonidis, who discontinued coverage of all obesity stocks. There might still be a path forward for Zafgen's pharmaceutical approach to treating a niche group of extremely overweight people, but its time horizon just got pushed out by several years.

This is because Zafgen has decided to pivot to a beloranib follow-up, ZGN-1061, which has not even entered clinical trials. On a call with analysts yesterday Zafgen played up the potential of this second-generation MetAP2 inhibitor, saying it had comparable efficacy to beloranib with a [much better safety profile](#) – according to mouse trials.

ZGN-1061 is wholly owned by Zafgen – Chong Kun Dang Pharmaceuticals was owed \$22.5m milestones plus a single-digit royalty on beloranib – and has a longer patent life. Zafgen now needs to show that the thromboembolic adverse events, including two patient deaths, that scuppered beloranib were not a class effect.

### Rollercoaster

Despite the US clinical hold that the deaths prompted, the sudden demise of beloranib comes as a surprise; there had been hopes for a way forward after beloranib's curtailed study convincingly hit both co-primary endpoints ([Zafgen surprises again, but bigger questions remain, January 20, 2016](#)).

But the rollercoaster ride for Zafgen's investors continued after the group failed to iron out a phase III design with the US FDA. The plan had included a risk-evaluation and mitigation strategy, to which the agency seemed receptive, but disagreement over the length of a study to confirm beloranib's potential in Prader-Willi syndrome (PWS) proved insurmountable.

Interestingly, in shifting focus to ZGN-1061 Zafgen is passing over two other MetAP2 inhibitor beloranib follow-ups: topline phase I data in obesity had been [announced for ZGN-433 in 2011](#), while ZGN-839 is still in preclinical evaluation to figure out its therapeutic window in NASH as well as abdominal obesity.

At least Zafgen had \$150.5m of cash at the half year, and after cutting 34% of its workforce expects this to last to the end of 2018, at which point it hopes to have ZGN-1061 phase IIa data in PWS under its belt to show prospective licensing partners. A two-part phase I trial in eight subjects is to begin next year.

### Market flops

If there remains a ray of hope for ZGN-1061 it cannot make up for the shadows that engulfed the obesity space when three once-promising oral drugs – Vivus's Qsymia, Arena's Belviq and Orexigen's Contrave – flopped in the market owing largely to lack of efficacy.

With them faded the latest hope of an oral, mass-market obesity treatment capable of generating blockbuster sales. Earlier hopes were dashed with the discontinuation of Wyeth's potent but toxic fen-phen in the 1990s, and the disappointment of Roche's Xenical, sunk by a nasty side-effect profile coupled with negligible efficacy.

The only one of the current crop of obesity drugs that still holds significant promise is Novo Nordisk's Saxenda, forecast to sell \$175m this year and \$791m in 2022, according to *EvaluatePharma's* sellside consensus. Still, this is injectable and available separately for diabetes, implying a different market dynamic.

This might point a way forward for others, such as Zafgen's MetAP2 inhibitors, which are also injected as well as targeting PWS, a small market segment of severely obese patients. Whatever the promise, however, investors with an appetite for obesity must settle in for the long haul.

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