Evaluate Vantage

June 25, 2018

ADA – Diabetes results resuscitate Zafgen, for now

Madeleine Armstrong

After two years in the doldrums Zafgen has been thrown a lifeline, with phase II diabetes data on its next-generation MetAP2 inhibitor, ZGN-1061, sending the group's stock up as much as 10% this morning.

But Zafgen needs a partner to take the project further and, with plenty of question marks remaining over ZGN-1061, finding one could be tough. Getting a bigger player on board could make or break Zafgen, which, with the exception of ZGN-1061, has a handful of preclinical assets and just $89m in the bank.

No dose response

Zafgen is claiming a win with ZGN-1061 in its phase II trial in overweight and obese type 2 diabetes patients, presented today at the American Diabetes Association meeting in Orlando. However, only one dose – 0.9mg, which the company is now calling the minimally effective dose – met the primary endpoint of change in HbA1c versus placebo at 12 weeks.

The other two doses tested, 0.05mg and 0.3mg, did not hit significance. If this in itself is not a problem the lack of consistency might be: the lower doses did not show a dose response, raising the possibility that the result with 0.9mg was a fluke. Moreover, in March the company added a 1.8mg cohort to the phase II trial, having earlier said this dose exceeded the threshold for response (*Zafgen gets one last fat chance, May 5, 2017*).

It appears that the response threshold argument is no longer relevant: the new 1.8mg cohort is due to yield results early next year, so perhaps things will become clearer then.

At least ZGN-1061's safety profile appears to be clean, albeit in small numbers of patients so far. This had been a worry after thromboembolic events with Zafgen's older MetAP2 inhibitor, beloranib, led to deaths and the suspension of its pivotal trial.

Zafgen executives today pointed to a lack of cardiovascular safety signals with ZGN-1061, including no meaningful elevations in levels of D-dimer, a marker of blood clotting.

But, with hopes of efficacy now resting on higher doses of ZGN-1061, investors and potential partners would do well to wonder whether a therapeutic window can be found.

Partner needed

Zafgen's chief executive, Jeffrey Hatfield, made it clear on a conference call today that the company had no intention of taking ZGN-1061 into phase III itself – a large pivotal diabetes trial would no doubt be prohibitively expensive for a group of its size.

But with the mixed data on ZGN-1061, plus a competitive diabetes sector, the question now is who else might want to take the asset on.

If approved, ZGN-1061 would likely be positioned as a third-line option in difficult-to-treat type 2 diabetics, who would otherwise be given insulin – a $20bn market, according to Zafgen.

The company also believes that the asset could improve the efficacy of other type 2 diabetes drugs used in earlier therapy lines, including GLP1 agonists and DPP-IV inhibitors. Preclinical data, also presented at the ADA meeting, found that ZGN-1061 plus Novo Nordisk's GLP1 Victoza lowered blood glucose and body weight better than either compound alone.

Promising preclinical data with ZGN-1061 in Nash, again at ADA, could help tempt a partner. But Nash is shaping up to be another crowded segment, with plenty of other players well ahead of Zafgen.

If the company can farm out ZGN-1061 it could concentrate on its next most advanced asset, ZGN-1258, another next-gen MetAP2 inhibitor that is poised to enter phase I in Prader-Willi syndrome by the end of the year.

However, if a big player does not come in for ZGN-1061, Zafgen will face a long road ahead for the rest of its projects, not to mention a funding crunch.

Study	Trial ID
Phase II proof-of-concept trial of ZGN-1061	NCT03254368

To contact the writer of this story email Madeleine Armstrong in London at madeleinea@epvantage.com or follow @ByMadeleineA on Twitter