Zafgen's beloranib generates MOA enthusiasm for severe obesity following insights from Phase II orphan study – experts

- HIAO data offers new evidence of peripheral effect on fat cells
- Dosing implications for only partially damaged hypothalamus
- Safety questions limited to risks of rare events, long term effects

Zafgen's (NASDAQ:ZFGN) beloranib has further MOA clarity generate physician enthusiasm for its Phase II potential in non-orphan obesity. New Phase II data in orphan indication hypothalamic injury-associated obesity (HIAO) shows convincing evidence that the drug has an effect on peripheral fat tissue, rather than a direct effect on the hypothalamus like other obesity agents, experts said, noting this bodes well for its risk/benefit profile.

Beloranib is an inhibitor of methionine aminopeptidease2 (MetAP2) that demonstrated significant weight loss in early trials, yet some sleep disturbance side effects and a hazy understanding of the drug's mechanism led to early concern about the drug's overall profile, this news service has previously reported. However, experts have now said the new efficacy demonstrated in patients with a completely damaged hypothalamus in the recently released HIAO study data, lends support to the theory that beloranib's primary target is peripheral fat tissue, strengthening the drug's safety and efficacy potential in a non-orphan obesity population.

The ongoing Phase IIb obesity trial is due to complete in June 2016, according to ClinicalTrials.gov.

Phase II HIAO results spur confidence

Although HIAO is an ultra orphan indication, the Phase II trial was an important step in understanding the drug's overall MOA which has implications for the general obesity population, experts said. HIAO patients have a completely damaged hypothalamus, the area of the brain that governs thirst and hunger.

A growing body of evidence suggests that obesity is related to some level of hypothalamic damage, even in the average person, said Dr Louis Aronne, director, Comprehensive Weight Control Center, Weill Cornell, New York. The Phase II HIAO results demonstrate that the drug's efficacy is derived from its action on fat tissue, and not on its activity on the hypothalamus, setting it apart from currently available medications and respective MOAs, he said.

Among 14 HIAO adults tested, the trial met its primary efficacy endpoint with twice weekly injections of 1.8mg of beloranib yielding mean weight loss of 3.4kg, compared to 0.3kg with placebo, over four weeks ($p = 0.01$), according to a 7 January press release. In addition, the treatment arm had an optional four week extension period, with an observed 6.2kg weight loss

over eight weeks, the release continued.

Other approved obesity medications include Vivus' (NASDAQ:VVUS) Qsymia (phentermine/topiramate) and Arena Pharmaceuticals' (NASDAQ:ARNA) Belviq (lorcaserin), OrexigenTherapeutics' (NASDAQ:OREX) Contrave (bupropion/naltrexone), and Novo Nordisk's (NYSE:NVO) Saxenda (liraglutide). Qsymia, Contrave and Belviq are all oral drugs that work on the CNS, while Saxenda is a subcutaneous glucagon-like peptide-1 (GLP-1) that improves blood glucose control.

Most of the drugs we have now work on the brain, so the efficacy seen in HIAO patients is unprecedented as available therapies have no effect on weight, said Dr Frank Greenway, chief, Outpatient Clinic, Pennington Biomedical Research Center, Baton Rouge, Louisiana.

While it is important to continue to collect for neurocognitive changes, the Phase II HIAO study did offer strong evidence to the idea that the drug is working specifically on the fat metabolism, said an obesity expert. There is also no reason to believe the drug's efficacy would be different in patients with more conventional types of obesity, said Dr Tom Elliott, medical director, BC Diabetes, Vancouver, British Columbia.

Efficacy in HIAO points to the fact that beloranib makes it easier for stored fat cells to be released, tapering hunger signals, said Aronne. However, the obesity expert was also careful to note that it is still possible that the drug is working directly on the brain and hypothalamus to some extent.

The Phase II study demonstrated the fact that the drug can work independent of an intact hypothalamus, said Dr Lee Kaplan, director, Obesity Metabolism and Nutrition Institute, Massachusetts General Hospital, Boston. However, beyond that, it is unclear whether beloranib works directly on fat metabolism or other mechanisms that influence fat metabolism indirectly, Kaplan said. It does not definitively prove the drug is working directly on white fat, or working on brown fat to indirectly activate burning of white fat, or if it's working on multiple mechanisms, he said.

Zafgen CEO Thomas Hughes also pointed to the reduction of inflammation (measured by C-reactive protein), increase in adiponectin, and reduction of leptin in treated HIAO patients as evidence that the drug is impacting fat regulating hormones.

Beloranib has been tested in six studies so far, and results from the HIAO study demonstrated consistent weight loss efficacy and metabolic changes in line with what Zafgen expects with beloranib, Hughes.

Safety downplayed, dose modification discussed

Importantly, there were no serious adverse events reported, experts interviewed said. In prior studies in Prader-Willi syndrome (PWS) -- a rare genetic disease linked that manifests in insatiable hunger typically leading to obesity -- beloranib's "murky" MOA, and its adverse effect on sleep patterns, were highlighted as concerns, but the HIAO data and dose modifications have

largely alleviated these worries, most experts said. However, they still pointed out that rare adverse events could crop up in a larger, longer-term trial in conventionally obese patients.

As the HIAO data indicates the drug is not working on the hypothalamus, this is a good safety development, as drugs that work peripherally tend to have fewer adverse events, said Dr Ken Fujioka, Scripps Clinic director of Nutrition and Metabolic Research and the Center for Weight Management, La Jolla, California.

As beloranib continues to be tested in patients with conventional obesity and diabetes, the peripheral action is a good indicator of safety, Fujioka said, adding that other medications that work on the central nervous system typically have to be very specific.

Beloranib appears to be well tolerated in PWS and HIAO patients so far, and the side effects observed so far seem to be mild and dose-related, Greenway said. In a previous Phase IIa study of beloranib in non-orphan obesity, 21 patients from a 2.4mg cohort withdrew due to sleep disturbances. Beloranib is being tested at 1.8 and 2.4mg in a Phase III trial in PWS, and is being tested at 1.2mg and 1.8mg in a Phase IIb trial in patients with obesity and diabetes.

The sleep disturbance side effect particularly appears to be dose-related, and the drug is likely to have good efficacy even at lower doses, said Greenway and Aronne.

Aronne noted that a higher level of risk is accepted in orphan patient populations compared to the general population, but as data on beloranib matures and more is understood about an appropriate dose for different patient populations, the drug's short-term safety profile seems more assured. In theory, patients with a mostly-functioning hypothalamus are better able to receive fullness signals, and demonstrated sufficient efficacy with an even smaller dose, further mitigating dose-related effects, said Aronne, who noted that the drug will still need rigorous Phase III trials to evaluate safety in the wider population.

In a conventionally obese population, the primary safety concern will be rare adverse events and cognitive disturbances, said Greenway and the obesity expert. PWS patients are cognitively impaired and may not be able to properly communicate certain side effects, said the obesity expert. Therefore, it is important to collect for a broad range of patient reported outcomes in non-orphan obesity, the expert continued.

Zafgen has a market cap of USD 1.1bn.

by Sony Salzman in New York