Zafgen of market capitalization of approximately $250 million

Finance, Investment

Zafgen Inc.

dedicated for improving the health and well-being of people affected by metabolic diseases including type 2 diabetes and obesity, lost more than 40% of companies investment after it was announced that FDA regulators were about to put hold on Zafgen’s primary drug, Beloranib. which in turn will affect all ongoing and planned trials for Beloranib. U. S.

Food and Drug Administration declared to halt all the trial held by Zafgen, after the death of two patients involved in the study. So the company suspended its developmental process on its lead drug Beloranib. Later when the company revealed that the death of two patients, who were their subject involved in the study, and was treated with the Beloranib for the Prader-Willi syndrome. But during their early announcement of the first patient death, the patient’s involvement as the control arm was not revealed. When the clinical trial was unblinded and it was confirmed that the deceased patient was receiving Beloranib. Shares of the Company, had a significant drop following the initial news of the patient’s death, lost more than 40% of their remaining value on October 16, 2015, representing a loss of market capitalization of approximately $250 million to investors, since the announcement of the patient’s death, with Beloranib. Prader-Willisyndrome as we all know is a complex genetic conditionthat affects many parts of the body. From childhood, this condition is noted bysymptoms such as weak muscle tone (hypotonia), feeding difficulties, poorgrowth, and delayed development.

Starting from childhood, the affectedindividuals develop an insatiable appetite, which then leads to chronicovereating (hyperphagia) and obesity. patients with Prader-Willi syndrome, particularly those withobesity, will also develop type 2 diabetes. Data from Phase II trial inorphan indication hypothalamic injury-associated obesity (HIAO) showsconvincing evidence that the drug has an effect on peripheral fat tissue, rather than adirect effect on the hypothalamus like other obesity agents, experts said, noting of this bodes well for itsrisk/benefit profile.

Beloranib a promisinginhibitor of Methionine Aminopeptidease2 (MetAP2) which demonstratedsignificant weight loss in early trials, But some sleep disturbance sideeffects and a hazy understanding of the drug's mechanism led to think earlyconcern about the drug's overall profile. However, experts said the newefficacy demonstrated in patients with a completely damaged hypothalamus in therecently released HIAO study data, providing support to the theory that beloranib'svery first and main target is peripheral fat tissue, strengthening the drug'ssafety and efficacy potential in a non-orphan obesity population. Phase II study opened thefact that, drug can work independent of an intact hypothalamus. However, beyondthat, it is unclear whether beloranib works directly on fat metabolism or othermechanisms that influence fat metabolism indirectly. It does not definitivelyprove the drug is working directly on white fat, or working on brown fat toindirectly activate burning of white fat, or if it's working on multiplemechanisms. Later study also pointed to the reduction of inflammation (measuredby C-reactive protein), increase inadiponectin, and reduction of leptin in treated HIAO

patients as evidence thatthe 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 efficacyand metabolic changes in line with what Zafgen expects with beloranib.

Major Safety concerns were downplayed and only dose modification wasdiscussed. Importantly, there were noserious adverse events reported, experts interviewed said. In priorstudies in Prader-Willi syndrome (PWS) — a rare genetic disease linked thatmanifests in insatiable hunger typically leading to obesity — beloranib's" misty" MOA, and its adverse effect on sleep patterns, which were highlightedas concerns, but the HIAO data and dose modifications have largely deviatedthese worries, revealed by experts.

However, they still pointed out that rareadverse events could crop up in a larger, longer-term trial in conventionallyobese patients. As the HIAO data indicates the drug is not working on thehypothalamus, this is a good safety development, as drugs that workperipherally tend to have fewer adverse events. As beloranibcontinues to be tested in patients with conventional obesity and diabetes, theperipheral action is a good indicator of safety, experts said, adding thatother medications that work on the central nervous system typically have to bevery specific. Beloranib was seen well tolerated in PWS and HIAOpatients so far, and the side effects observed so far seem to be mild anddose-related. In a previous Phase IIa study of beloranib in non-orphan obesity, 21 patients from a 2.

4mg cohort withdrew due to sleep disturbances. Beloranibis being tested at 1. 8 and 2.

4mg in a Phase III trial in PWS, and is beingtested at 1. 2mg and 1. 8mg in a Phase IIb trial in patients with obesity anddiabetes. The sleep disturbance side effect particularly appears tobe dose-related, and the drug is likely to have good efficacy even at lowerdoses. The overall higher level of risk is accepted in orphanpatient populations compared to the general population, but as data onbeloranib matures and more is understood about an appropriate dose fordifferent patient populations, the drug’s short-term safety profile seems moreassured. In theory, patients with a mostly-functioning hypothalamus are betterable to receive fullness signals, and demonstrated sufficient efficacy with aneven smaller dose, further mitigating dose-related effects, and was noted thatthe drug will still need rigorous Phase III trials to evaluate safety in thewider population. In a overall common obese population, the primary safetyconcern will be very rare adverse events and cognitive disturbances.

PWSpatients are cognitively altered and may not be able to properly communicatecertain side effects, said the obesity expert. Therefore, it is always important to collect for a broadrange of patient reported outcomes in nonorphan obesity, before predicting ahypothesis on any drugs efficacy, with a rigorous genuine study on populationranging from very small to larger population, by discussing all possiblepatients data outcomes.