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Zafgen, Inc. (ZFGN)

FDA Approval for a Deadly Drug? Fat Chance

Zafgen is a biopharmaceutical company on the brink of extinction. From its founding in 2005, Zafgen's "big idea," in the words of one piece of early press coverage, was to "fight fat by cutting off its blood supply." After licensing a drug called beloranib that was originally designed to inhibit angiogenesis (the development of new blood vessels) in order to treat cancer, Zafgen ultimately focused its development efforts on Prader–Willi syndrome (PWS), a rare genetic disorder in which a specific group of genes is missing or unexpressed, leading to an array of problems, including obesity and hyperphagia (extreme over-eating and food-seeking).

But Zafgen's work has ended in tragedy. In October, the company announced that a beloranib patient in its Phase 3 PWS trial died from pulmonary embolism – blood clots in the lungs' arteries. The FDA put a partial clinical hold on the drug but allowed Zafgen to continue the trial. Beloranib patients were only put back on the drug after being "screened for existing thrombotic [i.e. clotting-related] disease" and were then "regularly monitored" to ensure safety. Nonetheless, in December *another* beloranib patient died, *also* from pulmonary emboli, leading the FDA to apply a complete clinical hold. Moreover, Zafgen disclosed that other beloranib patients had experienced an additional seven (non-fatal) "thrombotic events." (Meanwhile, *no* placebo patients died, and *no* placebo patients suffered from thrombotic events.) With Zafgen's only well-developed drug candidate now revealed to be woefully dangerous – even in the face of enhanced screening and monitoring – its stock price collapsed.

But hope springs eternal. Last Wednesday, Zafgen released results from the Phase 3 PWS trial indicating that beloranib had statistically significant positive effects on weight and hyperphagia. The company's stock price rallied 79%, and multiple sell-side analysts issued new "buy" ratings. But this reaction is absurd. Nothing meaningful has changed: beloranib is highly dangerous but only modestly effective. While optimistic analysts think Zafgen can somehow "mitigate" the risks and placate the FDA enough to secure approval, beloranib is a drug that reduces weight by 4-5% at the expense of increasing patients' annual mortality rate by, according to our estimates, *a factor of 4 or more.* **Quadrupling the risk of death** in exchange for 5% weight loss is a monumentally bad bargain. Unlike those with late-stage cancer, for whom the health risks of angiogenesis inhibitors like beloranib make sense, PWS patients live relatively long lives, and Zafgen has already proven that, *even when it ramps up its screening and monitoring,* it does not know how to keep these patients safe. The FDA will not approve beloranib, and Zafgen is worth nothing more than the present value of its future cash balance, which we estimate is 65% below the current price.

I. Beloranib Is Unsafe

To understand the dangers of beloranib, it's important to put its body count in context. In Zafgen's Phase 3 PWS trial, patients randomized to the beloranib arms (corresponding to two different doses) received the drug for six months, followed by an additional six-month open-label extension in which they could opt to continue receiving the drug. Because the trial was cut short, however, many beloranib patients did not have time to receive the maximum twelve months of drug exposure even if they wanted to. Thus, although 2 dead patients out of 73 who received beloranib looks like a 2 / 73 = 2.7% death rate, we estimate that this corresponds to a 3.3% *annual* death rate – more than 20% higher.[1] At a 3.3% annual death rate, a staggering ~15% of beloranib patients (taking the drug twice weekly) would die over a five-year period.

What's the normal mortality risk faced by patients with PWS? Zafgen would like everyone to believe that it's very high, implying that beloranib's safety track record isn't as bad as it looks. But the best available evidence indicates that PWS, though clearly damaging to long-term survival, is a slow killer. We identified three recent studies of PWS that analyzed survival using the standard Kaplan–Meier method. The largest, drawing on the records of 425 PWS patients in Italy, showed that 20-year-olds with PWS had a *98% likelihood* of surviving the next five years and a 94% likelihood of surviving the next ten.[2] (The mean age in the beloranib arms of Zafgen's Phase 3 was ~19, with a standard deviation of ~5.5.) Two smaller studies produced similar results. One, based on 163 individuals with PWS in Victoria, Australia, estimated that 5-year survival from age 20 was 97%;[3] another, based on only 37 patients (also in Australia), estimated 82%.[4] Simply put, those with PWS who survive to early adulthood *should* have many years ahead of them.

Below, we use these three studies to estimate forward-looking annual death rates for PWS patients of different ages and take a sample-size-weighted average for each age. The typical

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[1] Zafgen has not provided enough information about how many patients opted to take beloranib during the open-label extension and for how long to allow us to adjust the death rate precisely. We assume that the first patient was enrolled on 10/1/14, that 67 patients were enrolled by 3/19/15 (based on comments from the 2015 Q1 earnings call), that 102 patients were enrolled by 5/12/15 (based on comments from the 2015 Q2 earnings call), and that the final 5 patients were enrolled by 5/15/15 (assuming the same pace of patients added per day as was seen between March and May). If enrollments were linear between those dates, then the average date of enrollment was 2/5/15. (Simply averaging the start and end dates of 10/1/14 and 5/15/15 produces a similar date: 1/22/15.) From that date to the date of the complete clinical hold (12/2/15), 0.82 years elapsed. We thus estimate the death rate per patient-year as 2 deaths / (73 patients x 0.82 years) = 3.3% per patient-year.

[2] Grugni et al., "The Italian National Survey for Prader-Willi Syndrome: An Epidemiologic Study," *American Journal of Medical Genetics Part A*, 2008. See Figure 3a.

[3] Lionti et al., "Prader-Willi Syndrome in Victoria: Mortality and Causes of Death," *Journal of Paediatrics and Child Health,* 2012. See Figure 1.

[4] Einfeld et al., "Mortality in Prader-Willi Syndrome," *American Journal on Mental Retardation,* 2006. See Figure 1.

rate for those in the relevant age groups is approximately 0.7%. Thus the death rate of PWS patients on beloranib is ~**4.7 times higher** than normal.

Prader–Willi Syndrome: Normal Death Rates by Age

Average annual death rate over following 5 years

Starting age	Grugni 2008 (*n* = 425)	Lionti 2012 (*n* = 163)	Einfeld 2006 (*n* = 37)	*n*-weighted average
15	0.3%	0.4%	0.0%	0.3%
20	0.5%	0.6%	3.8%	**0.7%**
25	0.8%	0.9%	0.0%	**0.7%**
30	1.7%	0.0%	1.8%	1.3%

Source: Grugni et al. 2008, Lionti et al. 2012, Einfeld et al. 2006, Kerrisdale analysis

Death rates shown are derived from published Kaplan–Meier survival curves. Note: 0% values are artifacts of small sample sizes. For instance, in Einfeld 2006, the survival curve implies that no patients die from age 15 to age 20 – obviously an imprecise estimate, but an indication of the relatively low risk of death.

Consistent with the conclusion that beloranib is deadly (but that PWS itself rarely is, at least in the short run), *zero* placebo patients died in the Phase 3 trial. Moreover, *both* beloranib fatalities had the same proximate cause – pulmonary embolism – while other beloranib patients experienced less severe but similar types of adverse events. Is this all just a big coincidence – a fundamentally innocuous drug with a run of bad luck? At times, Zafgen management has taken this tack, arguing that pulmonary embolism and thrombotic issues in general are common for those with PWS – so who's to say that beloranib is to blame?

This line of reasoning defies logic and common sense. Zafgen's preferred data source,[5] an unpublished analysis of 310 deaths tracked by the Prader–Willi Syndrome Association, indicates that 6% of PWS deaths result from pulmonary embolism – not a very high number. Of course, the probability of *two* dead patients *both* dying from pulmonary embolism purely by chance is 6% x 6% = 0.36% – odds of 277 to 1. And we calculate that, assuming an underlying PWS death rate of 0.7% per year, the probability of 2 out of 73 patients coincidentally dying from the *same* 6%-likely cause is vanishingly tiny – 0.03%, or odds of 3,520 to 1. These are not coincidences. In PWS patients – and potentially in others – beloranib increases the risk of death from pulmonary embolism *astronomically*. With these data in hand, what kind of doctor would risk prescribing this drug? What kind of regulator would allow it onto the market?

[5] Discussed e.g. on slide 8 of Zafgen's 2015 Q3 earnings presentation.

II. Drugs Like Beloranib Are Known to Cause Thrombosis

As previously mentioned, beloranib was originally intended to inhibit angiogenesis – the development of new blood vessels – to treat cancer. Not only is it intuitively plausible that a drug that affects blood-vessel function could lead to dangerous vascular side effects (like fatal blood clots); the risk was even identified ahead of time by a third party. Last March, Dr. Robert Howland wrote a short piece with the subtitle "The Story behind Beloranib,"[6] which noted some of the safety concerns (emphasis added):

> The safety of beloranib in particular will need to be evaluated carefully. Angiogenic factors have broad biological functions that are necessary for normal physiological functioning…Hence, angiogenesis inhibitor drugs used for treating obesity may have **many expected and unexpected adverse effects**. For example, the drug thalidomide was found to be an angiogenesis inhibitor more than 30 years after it was notoriously associated with major teratogenic effects. Other angiogenesis inhibitor drugs have been associated with bleeding, hypertension, proteinuria, and **fatal cardiovascular events**, and angiogenesis inhibition may impair wound healing and tissue repair.

Furthermore, angiogenesis inhibitors have been linked to thrombosis specifically. The National Cancer Institute's layman-oriented web page on angiogenesis inhibitors, answering the question, "Do angiogenesis inhibitors have side effects?" says, "Side effects of treatment with angiogenesis inhibitors can include problems with bleeding, **clots in the arteries** (with resultant stroke or heart attack), hypertension, and protein in the urine" (emphasis added). A 2009 review paper entitled "Thrombosis Associated with Angiogenesis Inhibitors" noted that "[m]any new biological agents with anti-angiogenic properties appear to be associated with an increased risk for thrombosis," with evidence implicating thalidomide, lenalidomide, semaxibin, prinomastat, bevacizumab, sunitinib, and sorafenib.[7] In short, beloranib's thrombosis problem is not out of left field; it's consistent with the history of other angiogenesis inhibitors.[8] The FDA won't fail to notice this pattern.

Zafgen's management denies that the track record of angiogenesis inhibitors is relevant because, it argues, the doses of beloranib used in its recent clinical trials are far too low to actually stop angiogenesis. In fact, while Zafgen *originally* believed that beloranib "[fought] fat by cutting off its blood supply," it later discovered a different mechanism of action unrelated to the blood. But there's nothing stopping a drug from having multiple effects on different parts of the body, and the same intrinsic properties that made beloranib a strong angiogenesis inhibitor at

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[6] Robert Howland, "*Aspergillus,* Angiogenesis, and Obesity: The Story Behind Beloranib," *Journal of Psychosocial Nursing,* 2015.

[7] Elice et al., "Thrombosis Associated with Angiogenesis Inhibitors," *Best Practice & Research Clinical Haematology,* 2009.

[8] Interestingly, a 2013 paper points to a possible mechanism by which beloranib might cause thrombosis. Beloranib is an artificial analog of a natural compound called fumagillin, and fumagillin has been found to stimulate eryptosis – red-blood-cell suicide – which, the authors note, "favours the development of thrombosis."

high doses are still there at low doses. Perhaps small amounts aren't enough to block blood-vessel growth outright but *are* enough to have other, subtler effects, which might accumulate over time. No one knows – certainly not Zafgen. But beloranib's history as an angiogenesis inhibitor, coupled with the propensity of such agents to cause thrombosis, is yet another uncomfortable "coincidence," suggesting that the drug is ineluctably dangerous and that the two deaths it caused were not flukes.

III. Beloranib Is Only Modestly Effective

For all the excitement that beloranib's Phase 3 results fostered, they're simply not life-changing. Over a six-month period, beloranib patients lost, on average, 4-5% of their body weight, while placebo patients gained 4%. No one knows whether this weight loss persists much beyond six months. The benefit, though real, is small, especially by the standards Zafgen had previously set for itself. In a 2010 interview with Xconomy.com, Zafgen CEO Thomas Hughes went so far as to argue that beloranib "will likely be a competitor for bariatric surgery" and "will need to show about an additional 20 percentage points of body weight loss beyond what patients get from a placebo." The article concludes:

> If Zafgen can reach its lofty goal later this year, it will be in a position to raise more capital, or strike a partnership, Hughes says. If not, then it might be time to throw in the towel.
>
> "If the molecule works the way we think it does based on animal studies, we're in good shape. If it isn't, then maybe we shouldn't be doing it," Hughes says.

Zafgen got only halfway to its goal of a 20-percentage-point advantage over placebo, at the cost of two dead patients. It is indeed time to throw in the towel.

Beyond weight loss, beloranib appeared to improve hyperphagia – the extreme overeating and sometimes dangerous food-seeking that drives obesity in PWS. Again, however, the benefit was real but modest. According to Zafgen, the improvement in behavior rose to the level of "at least moderate" (from the perspective of patients' caregivers) for approximately 44% of beloranib patients and 12% of placebo patients.[9] Moreover, instances of hyperphagia were actually *more* common among beloranib patients than placebo patients.[10] On one side of the scale, we have 4-5% weight loss and a 44% chance of "at least moderate" behavior improvement – neither of which may last much beyond six months. On the other side of the scale, we have a four-fold

[9] 52% in the 37-patient high-dose group and 36% in the 36-patient low-dose group. Source: Bloomberg transcript of Zafgen's 1/20/16 conference call.

[10] See slide 19 of Zafgen's 1/20/16 presentation. Hyperphagia occurs in 8.8% of placebo patients, 16.7% of low-dose beloranib patients, and 5.4% of high-dose beloranib patients, for a total beloranib rate of 11.0%.

increase in the risk of death (and an astronomical increase in the risk of death by pulmonary embolism). Is there any question which way the scales tip?

Ignoring this unpalatable trade-off, Zafgen bulls argue that, because Prader–Willi syndrome is an "orphan" ailment, the FDA will be lenient. But beloranib is only in the loosest sense a treatment for PWS specifically; it's really just one of several obesity drugs. Others, like Belviq, Qsymia, and Contrave, are already approved and available, though their efficacy for PWS in particular is unknown. (A private firm called Rhythm *is* developing a drug that directly addresses the genetic defect now thought to cause obesity in PWS.) Perhaps the FDA would err on the side of leniency for a drug aimed at a disease with a terrible prognosis and no alternative treatment, but beloranib isn't such a drug: people with PWS typically have decades, not months, to live, and other obesity-reducing drugs already exist, with more on the way. Beloranib is somewhat effective, but the benefits are trivial compared to the grievous dangers.

IV. There Is No Good Way to "Mitigate" Beloranib's Risks

On its conference call last week, Zafgen said it was "hopeful that with proper screening and monitoring protocols in place, potential thrombotic risk can be effectively managed." The sell side has picked up this idea and run with it, expressing delusional confidence in some as yet undefined "risk mitigation plan."

It all sounds a lot like the party line in October, when Zafgen first revealed that a beloranib patient had died. Striving to blame the death on everything but beloranib, Zafgen said it would screen patients for "existing thrombotic disease to make sure that none of these patients have the disease before we continue to dose" – implying that the dead patient was a victim of pre-existing but undetected disease, not beloranib.[11] Patients and their caregivers took comfort in the new precautions. One parent of an individual with PWS who was enrolled in the beloranib trial said, "The risk factor needs to be dealt with, but he's getting the blood tests and the ultrasound and if everything's ok, I have no problem putting him back on the drug."

Yet despite "the blood tests and the ultrasound" and other measures that Zafgen encouraged patients to have faith in, *another* beloranib patient died from pulmonary embolism in a matter of days. It is now glaringly obvious that Zafgen doesn't know what to look for. The countermeasures it came up with after one patient died didn't stop a second patient from dying of the same cause. Why should anyone – patients, doctors, or the FDA – trust that whatever new countermeasures Zafgen comes up with will prevent additional deaths? No one knows what's going wrong, so how can it be reliably "mitigated"? Since this is truly a matter of life or death, no animal models will suffice, but, by the same token, further human experiments are unethical. (Would you like to enroll in a trial of a deadly drug with modest benefits? It kills people at an alarming rate, and no one knows exactly why, but maybe if we give you a lower dose or

[11] Source: Bloomberg transcript of Zafgen's 10/16/15 conference call.

some anticoagulants, you won't die. Or maybe you will. Science is a messy business. Interested?)

V. Zafgen Is Worth ~$3 per Share

With beloranib on complete clinical hold and with no meaningful development pipeline,[12] Zafgen has no future. It does, however, have cash – $204 million as of 9/30/15. But it's not about to close up shop tomorrow and return that money to shareholders; it's going to keep trying to salvage beloranib, just as many other biopharma firms have wasted money on other lost causes. According to consensus estimates, Zafgen will burn $113 million from 2015 Q4 to 2016, reducing its cash balance to $91 million, or $3.33 per share.[13] Using a generous 8% discount rate, $3.33 at the end of 2016 is worth $3.07 today. Thus Zafgen's stock has at least 65% downside. The notion that has reanimated the stock – that beloranib is so strikingly effective that the FDA will take it off clinical hold and allow it onto the market despite all the risks – is a bizarre fantasy. Protecting patients from drugs like beloranib, with small potential benefits and huge, terrifying costs, is the FDA's most basic job, and the agency isn't going to stop doing it just to make a few investors happy.

[12] Zafgen's two non-beloranib drug candidates are both preclinical. Moreover, they both have the same mechanism of action as beloranib; given what happened to beloranib, they are likely non-starters.
[13] According to Capital IQ, consensus free cash flow is $(27.2)mm for 2015 Q4 and $(86.0)mm for 2016.

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