EQUITY RESEARCH FIRST GLANCE

RBC Capital Markets

RBC Capital Markets, LLC
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Outperform
Speculative Risk
NASDAQ: ZFGN
Price: USD 31.91

All values in USD unless otherwise noted.

May 28, 2015

Zafgen, Inc.

bestPWS Phase III enrolled; younger, higher BMI, high chance for positive Phase III

We view average patient's age (20) and BMI (40 kg/m2) as positives; reiterate our expectation for positive Phase III.

The news: Zafgen announced today the completion of enrollment into the US Phase III bestPWS trial for beloranib in 108 patients with Prader-Willi Syndrome (PWS). The trial is set to read out early in 1Q16, as previously guided. Zafgen also disclosed that the average patient's age is 20 and their BMI is ~40 kg/m2. We view this new piece of information as an important incremental positive for the stock.

The announcement of the completion of enrollment of the trial is not important in and of itself. What we view as a significant nugget of information is that the average patient enrolled in the trial has a BMI of 40kg/m^2 and is ~20 years old. And here is why: In their 4Q14 earnings call, Zafgen announced that they lowered the minimum BMI threshold from 30 to 27 in order to speed up trial enrollment. *Investors didn't like the change for two reasons and the stock reacted negatively*: **1)** investors rarely like clinical trial changes in the middle of any trial, let alone a pivotal one, and, as history has shown, *in most cases*, they're right not to, and **2)** including lower weight patients increases the clinical trial risk for beloranib, since it is (generally speaking) easier to show a weight loss benefit in a higher weight patient population, than in a lower weight one.

So, this change with the newly decreased BMI entry threshold could have potentially enrolled a sizeable number of patients who could have significantly lowered the overall average BMI. In the prior Phase II PWS trial in which the patient population had an average BMI of ~31, weight loss achieved with beloranib was not statistically significant. However, with an average BMI of 40, bestPWS is in line with their previous trials in normal obese patients and HIAO patients (see Exhibit 1 on page 2), which all had statistically significant weight loss, and with treatment durations that were much shorter than the 6-month bestPWS trial. Additionally, the average age of the enrolled patients is 20, which is lower than patients in earlier trials. On average, it is easier for a younger patient to achieve weight loss, vs. an older one.

Therefore, we view the announcement of the high average BMI and younger age as an incremental positive for ZFGN. We believe there is a greater probability for beloranib to elicit statistically significant weight reductions in a PWS population that is younger and heavier.

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What's next for ZFGN: 1) Submit IND for oral ZGN-839 program in NASH/T2DM, mid- 2015; 2) Initiate second PWS trial (ZAF-312) in EU, mid-2015; **3) Interim Ph IIb ZAF-203 data in severe obesity, late 2015/early 2016**; **4) 6-month Ph III bestPWS readout, early 1Q16**; 5) File IND for second-generation MetAP2 inhibitor, 1Q16; 6) Initiate Phase III program in HIAO, 2016; 7) Complete ZAF-203 severe obesity trial, 2016.

Our thesis on ZFGN: **A very impressive injectable drug for obesity**…Beloranib acts via a novel mechanism of action (MOA) to lead to rapid and impressive weight loss in the obese patients it has been tested on in early-stage Phase I and II trials. Using a different MOA than the ones used by the weight-loss drugs currently on the market, this methionine aminopeptidase 2 (MetAP2) inhibitor leads to significant weight loss (up to 10% of body weight) in just 12 weeks. Two factors make this efficacy even more impressive: 1) it was achieved without the benefit of any diet or exercise; and 2) this weight loss did not seem to plateau after 12 weeks of treatment, suggesting that even more weight loss could be achieved with longer treatment.

…but it will not get to the market for obesity first: However, and despite this impressive efficacy, Zafgen has decided to not go with obesity as its first indication for beloranib, but rather to test it in rare diseases instead. If successful, this strategy may get the drug to the market faster, in addition to other benefits, including premium pricing.

Exhibit 1: Average BMI and weight loss across beloranib trials

	Phase Ib ZAF-101	Phase IIa ZAF-201	Phase IIa ZAF-221	Phase II ZAF-211	Phase III bestPWS
Patient population	general obese individuals		HIAO	PWS individuals	
# of patients enrolled	25	160	14	17	108
% female	100%	94%	64%	65%	~50%
Average age (years)	46.0-49.9	48.4	31.8	33.9	~20
Average BMI (kg/m^2)	34-36.4	38	42.8	31.4	**~40**
Length of treatment	4 weeks	12 weeks	4 weeks	4 weeks	29 weeks (6 months)
Treatment arms	placebo (n=6), 1.0 mg (n=6), 2.0 mg (n=5), 4.0 mg (n=4)	placebo (n=36), 0.6 mg (n=34), 1.2 mg (n=31), 2.4 mg (n=15)	placebo (n=6), 1.8 mg (n=8)	placebo (n=6), 1.2 mg (n=5), 1.8 mg (n=6)	placebo, 1.8 mg, 2.4 mg
Average weight loss	1.0 mg: -4.3%; 2.0 mg: -4.5%; 4.0 mg: -6.5%; placebo: -1.2%	0.6 mg: -5.4%; 1.2 mg: -6.7%; 2.4 mg: -10.7%; placebo: -0.4%	1.8 mg (4 wks): -2.7%; 1.8 mg (8 wks): -4.9%; placebo (4 wks): -0.2%	pooled beloranib: -1.27%; placebo: +0.34%	
p-value	all p<0.001	all p<0.0001	p=0.01 at 4 wks	p=0.17	

Source: Company reports

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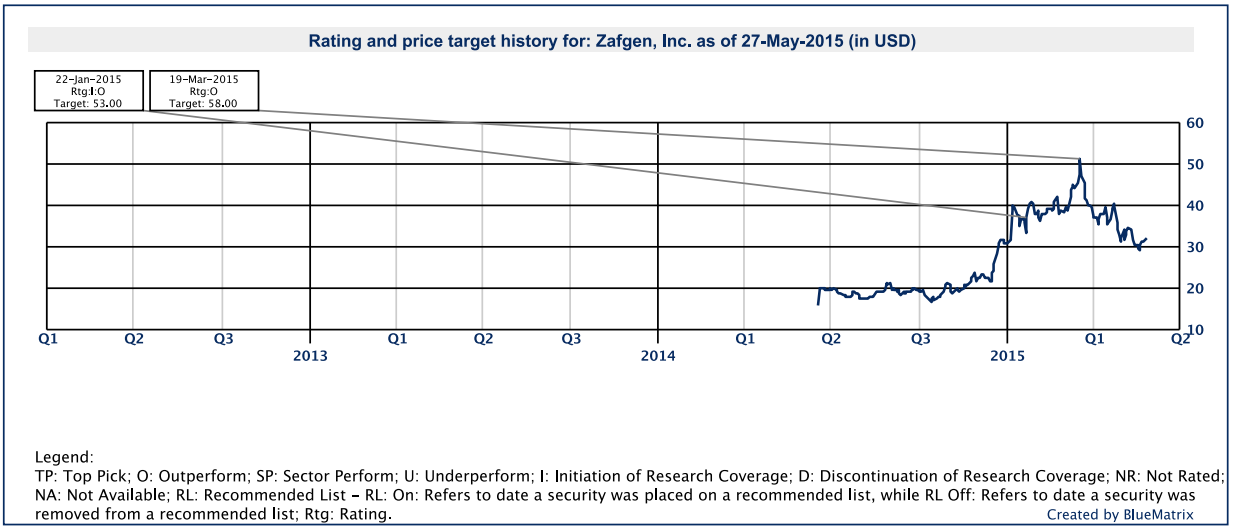

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