Zafgen

ZFGN : NASDAQ : US$17.74

BUY

Target: US$36.00

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COMPANY STATISTICS:

Forecast Return:	102.9%
52-week Range:	17 - 20
Shares Out (M):	22.7
Market Cap (M):	US$402
Avg. Daily Vol. (000s):	32
Cash (M):	38
2014E Burn:	($39)
2015E Burn:	($52)
# Analysts:	3
Avg. Target:	37
# BUY:	3
Shares Short (M):	0.7
Days to Cover:	15.5

EARNINGS SUMMARY:

FYE Dec		2013A	2014E	2015E	2016E
EPS:		(2.98)	(2.26)	(2.26)	(2.13)
EPS:	Q1	(0.77)	(0.29)A	-	-
	Q2	NA	(0.44)	-	-
	Q3	NA	(0.77)	-	-
	Q4	NA	(0.77)	-	-
Total		(2.98)	(2.26)	(2.26)	(2.13)

SHARE PRICE PERFORMANCE:

Source: Interactive Data Corporation

COMPANY DESCRIPTION:
Zafgen is focused on novel treatments for metabolic diseases. Its lead product is beloranib, an injectable MetAP2 inhibitor in Phase 2/3 development for various conditions related to obesity. It will have orphan drug status for both Prader-Willi Syndrome and craniopharyngioma, but is also being developed for severely obese individuals. Zafgen is headquartered in Cambridge, MA.

All amounts in US$ unless otherwise noted.

Life Sciences -- Specialty Pharmaceuticals

INITIATING WITH A PHAT BUY

Investment recommendation

Zafgen is targeting specific forms of obesity with a novel drug that has shown dramatic effects on weight. Thus, beloranib is targeting the severely obese – for two orphan indications in Prader-Willi Syndrome and craniopharyngioma, and in morbidly obese individuals. With proof-of-concept data in hand, and although the timelines may seem long, we can justify our $36 target based on the multibillion potential for this drug.

Investment highlights

High efficacy. All trials show beloranib with very high efficacy and a fast onset. The most compelling is the Phase 2 in severe obesity where the 2.4mg dose showed 10.9% weight loss at 12 weeks. The hope is for higher loss at 24 and 52 weeks. The goal would be to get into the range of the surgical approaches at >20%. With novel mechanisms come potentially unforeseen safety hurdles and although everything looks clean so far, it is something to watch.

Orphan indications allow premium pricing. Unlike current oral medications such as Belviq ($4/day) and Qsymia ($6-8/day), the PWS and craniopharyngioma indications have only ~6,000-8,000 patients in the US. So as long as efficacy pans out, it should support the $150,000/patient/year we've modeled. Only 25% penetration could produce >$500M in revenue. We assume ZFGN will use its backup molecule in severe obesity (17M US patients) so it doesn't have a pricing problem.

Data-rich 2015. With the IPO proceeds, Zafgen should be able to have: 1) four-week P2a data in craniopharyngioma in Q1'15; 2) six-month P3 PWS data in Q4'15; and 3) six-month P2b data in severe obesity in Q4'15.

Valuation/Risks

We use a discounted P/E model to derive our $36 target; we apply a 25x multiple to our 2021 EPS estimate of $7.74 discounted at 25% for 6.5 years. Risks include: slow recruitment to clinical trials, hitting an efficacy plateau in trials beyond 24 weeks, and/or failure to gain FDA approval.

INVESTMENT THESIS

Zafgen was founded in 2005 and has now shown powerful proof-of-concept data with its drug beloranib in treating various forms of obesity. With the proceeds from its recent IPO, it should be able to generate even further de-risking data in all three of its indication in 2015. We like the prospects for both the stock and the drug for several reasons:

1. **Powerful efficacy**. In every trial conducted to date (in both human and animal models) beloranib has shown very rapid and intense weight loss. There is no question the drug is having a powerful effect. The most impressive was the 10.9% weight loss at 12 weeks in the Phase 2a severe obesity trial. The big unanswered question is how much more weight loss can be obtained when tested in trials longer than 12 weeks. Not only was there high weight loss, but there were impressive cardiovascular benefits on triglycerides, LDL HDL, blood pressure and CRP levels – after only 12 weeks.

2. **Limited adverse events…..so far.** With any obesity drug, the safety hurdle will be quite high with the FDA. And so far the only noticeable side effects are sleep disturbance, with some nausea and vomiting (which would be expected with such rapid weight loss). These were primarily at the 2.4mg dose (injected twice weekly subcutaneously). So the dose that is likely to be taken into Phase 2b in severe obesity will be 1.9mg. For PWS, however, doses of 2.4mg and 1.2mg will be studied in Phase 3. There do not appear to be any cardiovascular side effects, and in fact, as mentioned above, beloranib has shown impressive cardiovascular benefits. However, with any novel mechanism (especially one like this that has not been fully elucidated) comes the potential for novel side effects. And although no signals have been reported, as more patients are exposed to the drug, it is something to watch for as more rare events could possibly be uncovered.

3. **Orphan indications support expedited FDA processes and high pricing power**. Because there are so few options for Prader-Willi, and craniopharyngioma (hereafter abbreviated CP) patients, beloranib should play well with the FDA for an expedited approval. And indeed after only one small (n=17) proof-of-concept trial in PWS, the FDA is allowing Zafgen to go immediately into a Phase 3 program – one in the US and one in Europe with a total of 240 patients. In addition, the agency is allowing the company to use primary endpoints of improvement in either total body fat mass or hyperphagia-related behaviors. Weight loss will be used as a secondary endpoint. Assuming all goes well and with only about 6,000-8,000 PWS patients, we think this type of product could see pricing in the range of other orphan drugs of ~$150,000 per patient per year and that's what we've used for modeling purposes in both PWS and CP.

4. **Data-rich 2015**. With three data readouts slated for 2015, it should be a good year for catalysts to move the stock: 1) four-week Phase 2a data in craniopharyngioma in Q1 2015 in 14 patients; 2) initial six-month Phase 3 PWS data in Q4 2015; and 3) initial six-month Phase 2b data in severely obesity diabetics in Q4 2015.

5. **Novel mechanism of action with pleiotropic effects**. Beloranib was in-licensed from the Korean company CKD that was examining inhibition of methionine amino peptidase 2i (MetAP2i). The effects on fat metabolism was somewhat stumbled upon as the drug was initially being screened for activity against solid tumors. But the doses needed to shrink tumors (through an anti-angiogenic effect) were almost 500- to 1,000-fold

higher than what Zafgen is now using for obesity. It appears that the mechanism by which the drug exerts its effect has to do with the fact that MetAP2 seems to coordinate a cell's entire metabolism by acting as a nutritional sensor. The way it does this is believed to involve attenuation of ERK phosphylation and pleiotropic (multiple) effects on gene expression, leading to hormonal changes that result in reduced food intake, reduced fat synthesis, increased fat burning, reduced cholesterol and reduced inflammation. It perhaps sounds too good to be true but the clinical data always trump mechanistic hypotheses and the drug clearly is inducing rapid weight loss. The only caveat is that with novel mechanisms come the potential for unforeseen adverse effects – even rare ones – that might not be seen until the drug is tested in a far greater number of individuals for longer periods of time. But it *is* known that the drug at doses being studied has neither anti-angiogenic effects nor any direct cellular toxicity.

6. **Differentiation from current obesity drugs/surgical options**. Beloranib should fit nicely in between the currently available oral medications for obesity that have limited efficacy but are convenient oral pills and the more invasive surgical procedures that lead to greater weight loss but are riskier and much more costly.
7. **Injection mitigates *a priori* abuse concerns**. The fact that beloranib is a twice-weekly injection may also allay some FDA concerns that the drug would be abused among individuals that simply wanted to shed a few pounds.
8. **NCE patents provide longevity of exclusivity well beyond orphan exclusivity**. Zafgen already has several key issued and pending patents that expire in 2019, 2029, and 2031.
9. **Owns 100% rights worldwide**. Other than a single-digit royalty owed to CKD, Zafgen owns worldwide rights to the compound. This provides excellent economics if it launches the orphan indications itself in the US and could choose to partner for European rights and/or a severe obesity claim.
10. **Strong management team**. As detailed in the back of this report, Zafgen has assembled an impressive management team on both the R&D/regulatory and commercial sides of the business. We find it comforting that such experienced individuals have chosen to come to Zafgen since it signals to us that all of them see the same type success for the molecule and hence upside for the stock that we do.
11. **Plenty of cash.** With the recent IPO, Zafgen should have about $100M in cash, which should be sufficient to last into 2016.

VALUATION

Because we don't foresee Zafgen being profitable until 2019 or so, we don't think a DCF approach to valuation is warranted. Therefore as shown below, we simply use a discounted multiple approach. For fast-growing companies with new products with long life cycles, we think a 20x multiple off forward-year earnings is appropriate. And we usually like to use a 25% discount rate on products not yet having completed Phase 3. Therefore, applying 20x to our 2021 EPS estimate and discounting it back 6.5 years (for a 12-month target) yields our $36 price target. Because there are those who may disagree with our choice of multiples, years of earnings, and choice of discount rate, we present the sensitivity analysis in the two tables below.

Figure 1: Price target sensitivity analysis by year of EPS estimates

	2019	2020	2021	2022
PE multiple	20.0x	20.0x	20.0x	20.0x
EPS	$3.29	$6.00	$7.74	$12.33
Total	65.73	120.05	154.90	246.58
Discount Rate	25%	25%	25%	25%
Discount Years	4.5	5.5	6.5	7.5
Price Target	$24	$35	**$36**	$46
Current price:	$17.95	$17.95	$17.95	$17.95
Return	34.1%	96.0%	102.3%	157.7%

Source: Canaccord Genuity estimates

Figure 2: Price target sensitivity analysis by multiple and discount rate

2021 EPS:	$7.74		Multiple					
Discount Period:	6.5		10.0x	15.0x	20.0x	25.0x	30.0x	35.0x
		10.0%	$42	$63	$83	$104	$125	$146
		15.0%	$31	$47	$62	$78	$94	$109
	Discount	20.0%	$24	$36	$47	$59	$71	$83
	Rate	25.0%	$18	$27	**$36**	$45	$54	$64
		30.0%	$14	$21	$28	$35	$42	$49
		35.0%	$11	$17	$22	$28	$33	$39
		40.0%	$9	$13	$17	$22	$26	$30

Source: Canaccord Genuity estimates

REVENUE & MARKET MODELS

We have modeled each of the two orphan indications for beloranib priced at $150,000 per patient per year, but we have assumed that the follow-on molecule will eventually be approved for an indication of more general severe obesity and that would be priced at a much lower $10,000 per patient per year. We think this level of pricing is reasonable given that Zafgen has already shown benefits that go well beyond simple weight loss – in cardiovascular risk factors as well as behavioral benefits in PWS patients. We doubt it would ever be able to be proven in a clinical trial setting, but if beloranib shows enough benefit on these other risk factors, it could very easily lead to a survival benefit, given that the average life expectancy for PWS patients is only in their 30s.

Although precise prevalence is not really known, we start with 7,500 patients in PWS in 2014 (calculated based on prevalence of 1 in 40,000 Americans) and grow that 2% per year. Similarly, we start with 6,000 CP patients in 2014 and grow that population at the same 2% per year. We assume beloranib launches in 2018 in PWS and in 2019 in CP. Hitting only 28% penetration in 2023 in PWS and 21% penetration in CP in 2023 would lead to estimated US revenues of $769 million. We also foresee international revenues of $384 million in 2023, but this is much trickier to predict because it is unclear whether Zafgen would have the resources and/or the desire to set up the infrastructure in Europe and the rest of world to sell the drug itself, or whether it would enlist a partner to sell it. We have implicitly assumed a partner and that's why the international numbers are about half of the US figures. But this is still a moving target, and so at this point we have not included ROW revenues in our P&L, instead leaving that as potential upside.

For the severe obesity indication, because beloranib could not command the same orphan pricing of $150,000 per patient per year, one could imagine two scenarios: 1) that beloranib is the molecule that gains the indication and when approved, Zafgen simply lowers the price dramatically and foregoes the revenues in the orphan indications, 2) Zafgen chooses to use its backup compound for the severe obesity claim, this allowing differential pricing between the two different molecules. For modeling purposes, we have assumed the later scenario. We've also assumed a launch in 2020 and that Zafgen does not partner the product, but simply gears up its own sales force using the profits from the previously approved orphan indications. As with the orphan indications, we have not yet included international revenues for the severe obesity claim, for additional potential upside. According to Finkelstein et al., there are currently 17 million severely obese individuals in the US; so we used that number as our starting point and grew it 2% a year…but one could certainly posit an argument that it will grow even faster than that. So with only miniscule penetration of 0.4% in 2023, it would generate $955 million in revenue. All of this will be contingent of course, on the ultimate long-term efficacy of the molecule and we think it needs to get somewhere north of 15% weight loss at one year in order to command the type of pricing we've assumed and generate the kind of revenue we've modeled.

All of this is shown in the two figures below.

Figure 3: Revenue estimates

	Beloranib		Son of Beloranib	TOTAL ZAFGEN REVENUE
	PWS	Cranio	Severe Obesity	
2017E				
2018E	121.8			**121.8**
2019E	260.8	104.3		**365.2**
2020E	307.3	167.6	194.4	**669.3**
2021E	359.0	203.5	416.5	**978.9**
2022E	416.6	243.5	669.0	**1,329.1**
% Growth				
18E/17E				
19E/18E	114.2%			**199.9%**
20E/19E	17.8%	60.7%		**83.3%**
21E/20E	16.8%	21.4%	114.2%	**46.3%**
22E/21E	16.0%	19.7%	60.7%	**35.8%**

Source: Canaccord Genuity estimates

Figure 4: Zafgen market model

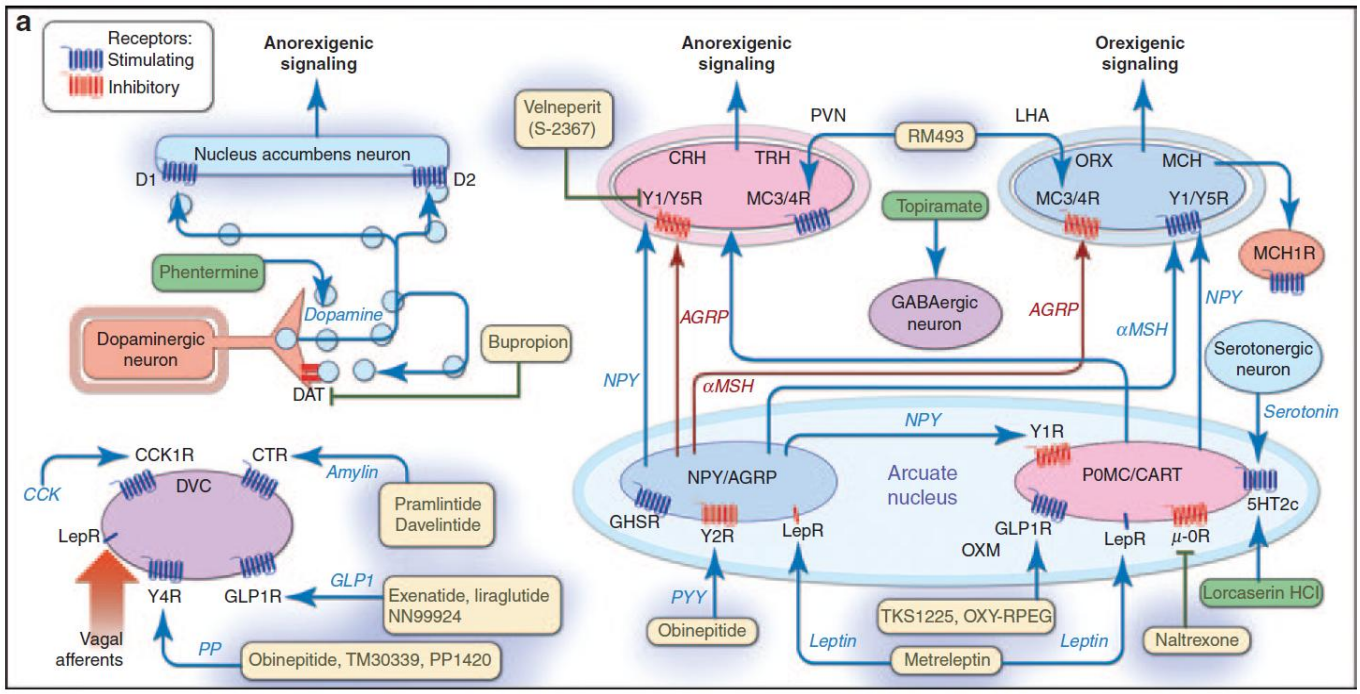
Zafgen Market Model	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
Patients with Prader-Willi Syndrome (PWS)	7,500	7,650	7,803	7,959	8,118	8,281	8,446	8,615	8,787	8,963
% Growth		*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*
% Treated with Beloranib					**10.0%**	**20.0%**	**22.0%**	**24.0%**	**26.0%**	**28.0%**
Patients Treated with Beloranib					812	1,656	1,858	2,068	2,285	2,510
Patients with Craniopharyngioma	6,000	6,120	6,242	6,367	6,495	6,624	6,757	6,892	7,030	7,171
% Growth		*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*
% Treated with Beloranib						**10.0%**	**15.0%**	**17.0%**	**19.0%**	**21.0%**
Patients Treated with Beloranib						662	1,014	1,172	1,336	1,506
Total Orphan Treated Patients					812	2,319	2,872	3,239	3,620	4,016
Beloranib Cost per Year					$150,000	$157,500	$165,375	$173,644	$182,326	$191,442
Beloranib revenue ($M)					**$122**	**$365**	**$475**	**$562**	**$660**	**$769**
ROW Revenue						**$183**	**$237**	**$281**	**$330**	**$384**
Total ORPHAN WW Revenue					**$122**	**$548**	**$712**	**$844**	**$990**	**$1,153**
Patients with Severe Obesity	17,264,500	17,609,790	17,961,986	18,321,226	18,687,650	19,061,403	19,442,631	19,831,484	20,228,113	20,632,676
% Growth		*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*	*2.0%*
% Treated with Beloranib							**0.1%**	**0.2%**	**0.3%**	**0.4%**
Patients Treated with Beloranib							19,443	39,663	60,684	82,531
Total Severe Obesity Patients							19,443	39,663	60,684	82,531
Son of Beloranib Cost per Year							$10,000	$10,500	$11,025	$11,576
Son of Beloranib revenue ($M)							**$194**	**$416**	**$669**	**$955**
Total ROW revenue for severe obesity								**$208**	**$335**	**$478**
Total Severe Obesity							**$194**	**$625**	**$1,004**	**$1,433**
TOTAL ZAFGEN REVENUE					**$122**	**$548**	**$907**	**$1,468**	**$1,994**	**$2,586**
% growth						*350%*	*66%*	*62%*	*36%*	*30%*

Source: Canaccord Genuity estimates; IMS

WEIGHT REGULATING MECHANISMS

Weight regulating mechanisms are extremely complex and we won't even attempt to try and explain them here (mostly because we ourselves don't understand all the complexities). But it is clear that there is no one single control mechanism. The figure below, from a 2014 publication, depicts just how complicated and intertwined the regulatory pathways are. Many of the drugs currently used for weight loss and ones in development are shown on this slide but many are not.

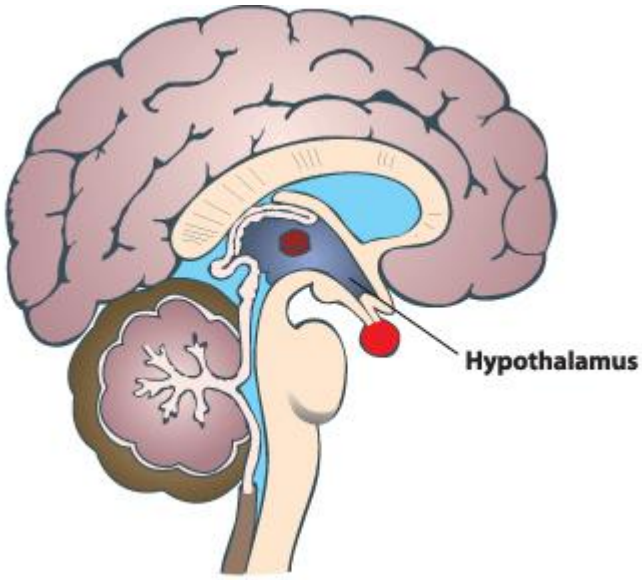
Figure 5: Weight regulation is extremely complex



Source: Clinical Pharmacology & Therapeutics | VOLUME 95 NUMBER 1 | January 2014 **53**

The hypothalamus (located within the brain near the brainstem as shown in the Figure 6) plays a central role in regulating metabolism as it is the site of integration of anorexigenic (loss of appetite) and orexigenic (an increase in appetite) signaling. One of the most important functions of the hypothalamus is to link the nervous and endocrine systems via the pituitary gland. Most current obesity treatments target pathways involved directly or indirectly with the hypothalamus and associated systems.

Figure 6: Location of the hypothalamus within the brain



Source: http://wiki.addictiontreatmentmagazine.com/medical/hormones/hypothalamus/

Beloranib, unlike most obesity drugs, does not act within the brain, but acts on the liver and adipose tissue; it is an inhibitor of MetAP2 (methioninine amino peptidase) and is believed to act most directly on the ERK pathway as discussed in greater detail below.

METAP2 INHIBITION: BELORANIB MECHANISM OF ACTION

Beloranib is a methionine aminopeptidase 2 (MetAP2) inhibitor. MetAP2 is a ubiquitous intracellular enzyme that serves a general function of cleaving the N-terminal methionine (an amino acid) off of proteins right after they are created by ribosomes. There is another MetAP, called MetAP1. This methionine is always the first amino acid of every protein that is made in a cell (coded for on the messenger RNA molecule by "AUG," also known as the "start codon" because it tells the ribosome to put the amino acid methionine in the first position). After the full-length protein is completely synthesized by the ribosome, this initial methionine is immediately cleaved by MetAP in about 80% of all newly synthesized proteins. But this explanation is still far from obvious how a drug that inhibits MetAP2 would work for obesity.

Oddly enough, and although it plays this general central function in all of protein synthesis, MetAP2 is now also known to play a key role in angiogenesis. Angiogenesis is the growth of new blood vessels, which is critical to the spread of solid cancerous tumors (because without a fresh blood supply, a tumor cannot grow or spread). There are natural anti-angiogenic compounds, one of which is fumagilin. It targets and inhibits MetAP2. Beloranib is a structural analogue of fumagilin. In fact, it was this anti-angiogenic activity (as an oncolytic agent) of beloranib that led to its initial creation by the Korean company CKD. It never panned out as a cancer drug, but in its early development, a rapid weight loss effect was noticed. And it is now being dosed at levels 500-1,000x less than what was initially being used in the oncology setting. But this still doesn't explain how beloranib works on obesity.

In 2004, fumagilin (of which beloranib is an analogue) was shown to create a novel protein-protein interaction between MetAP2 and a protein originally known as ERK1 (extracellular signal regulated kinase 1) – one member of a class of molecules known as MAP kinases. This complex reduces the activation date of ERK1, which is now hypothesized to have strong effects on fat metabolism.

Like all of the "mitogen-activated protein kinases", ERK affects certain proteins and processes in response to particular stimuli that get applied to any given cell type. Many of these signal transductions are involved in proliferation, differentiation, and metabolism. ERK can be viewed to function as a "nutritional sensor". In 2005, ERK1 homozygous knockout mice were used to establish a link between ERK1 and the development of adipose (fat) tissue. In the publication, the authors concluded that:

"Mice lacking ERK1 have decreased adiposity and fewer adipocytes than wild-type animals. Furthermore, ERK1^{-} mice challenged with high-fat diet are resistant to obesity, are protected from insulin resistance, and have a higher postprandial metabolic rate."

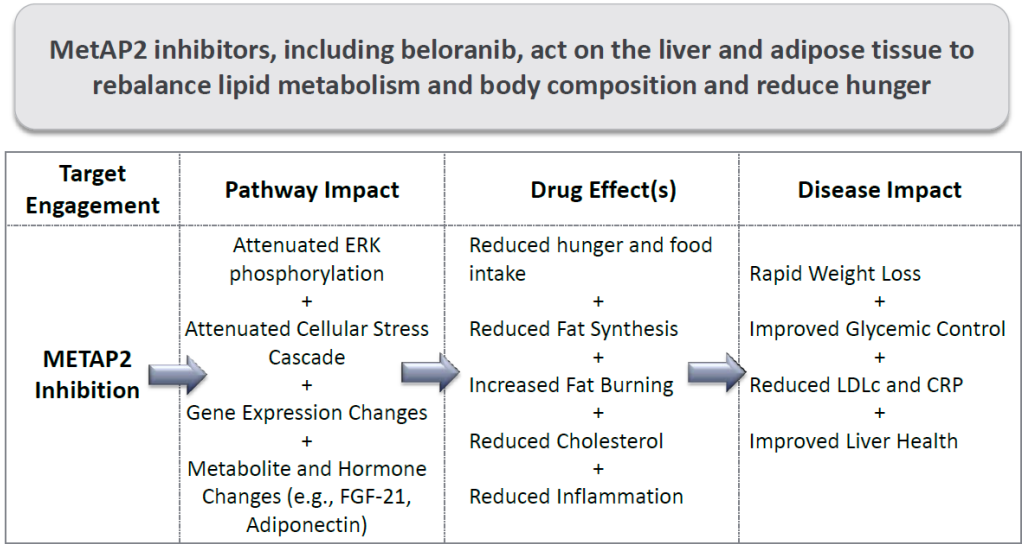
Source: http://diabetes.diabetesjournals.org/content/54/2/402.long

In animal models, beloranib has consistently been shown to increase fat oxidation and decrease inflammation. On the toxicity side, beloranib is known to inhibit spermatogenisis and also be teratogenic. So it will likely be a "Category X" drug, but that shouldn't impede its approval – especially in the orphan indications.

Generally speaking, this novel mechanism for beloranib, although not yet fully elucidated, is believed to work by re-establishing a balance to the ways the body packages and metabolizes fat. Inhibitors of MetAP2 attenuate ERK1 activity, which in turn reduces the production of new fatty acid molecules by the liver and help to convert stored fats into useful energy. Several hormones (such as leptin, adiponectin and fibroblast growth factor-21) that are well known to be involved in control of body weight, fat metabolism, and glucose metabolism, have been shown to be affected by beloranib. Treatment with beloranib results in a very fast fat catabolism and hence rapid and significant weight reduction.

In the Phase 2a study in severely obese individuals, beloranib showed an impressive and extremely rapid weight loss after only 12 weeks of 10.9% at the highest dose – see figure below. Whether patients continue to lose weight beyond 12 weeks remains to be seen in the currently planned, longer (6-12 months) studies, but the early signs as well as animal data are extremely promising. Its main drawback is that it is a twice-weekly subcutaneous injection and hence it will probably be reserved for individuals with very high BMIs over 40 kg/m^2.

Figure 7: Zafgen's general view on the mechanism of action for beloranib



Source: Company presentation

CURRENT US MARKET

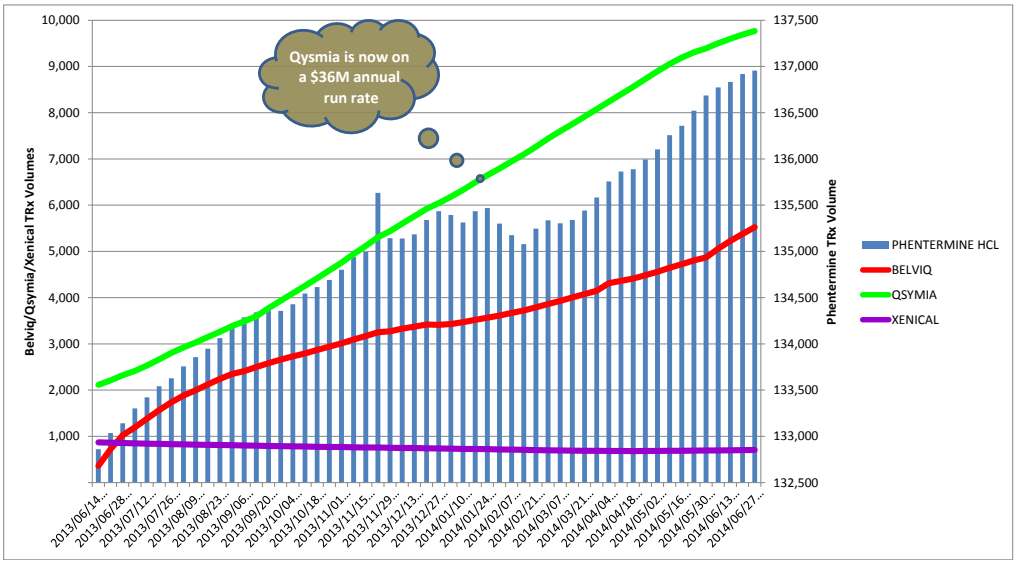
Currently marketed anti-obesity drugs

Everyone is searching for the magic pill that lets them eat excessively and lead sedentary lives without suffering from excessive weight gain. In the past decade, there have been a number of drug products on the market that either produce minimal to no long-term results or proved to have serious adverse effects. The only branded pharmaceutical compounds on the market have two distinct mechanisms:

- *Hunger suppression* – **Meridia** (sibutramine) increases the feeling of satiety by increasing the level of neurotransmitters, such as serotonin. However, it was pulled off the market in 2010 due to a controversial cardiovascular risk signal and only lowered body weight by 3-5%. **Phentermine** (highly genericized) has been on the market for over a decade and lowers weight by about 3.8-4.4% over 6 months. **Qsymia** (a combination of phentermine and topiramate sold by Vivus) and **Belviq** (lorcaserin developed by Arena and partnered with Easai) are two recently approved drugs that are doing OK on the market, but they too have limited efficacy. Qsymia lowered weight by 6.6-8.6% over 12 months in clinical trials. Belviq showed only a 3-3.3% weight loss at 12 months. Orexigen's **Contrave** (a combination of buproprion and naltrexone) now has a PDUFA date of September 11, 2014 and drops weight by about 10-15%. It was the only one of the recent drugs that FDA required to conduct a cardiovascular outcomes trial, and now that that has been successfully completed, we see no reason why it shouldn't get approved in September. It will be launched by Orexigen's partner, Takeda. **Byetta** is only approved for diabetes, but it suppresses hunger and can show weight loss, although anecdotal data suggests that weight loss is transient and not widespread. There are also several drugs that are used off-label like Adderall XR for example.
- *Fat absorption reduction* – **Xenical** (orlistat) and **Alli** (also orlistat but over-the-counter) inhibit lipase, which is an enzyme that breaks down and digests fat in the gut. When taken with meals it prevents 25%-30% of dietary fat from being absorbed. Patients see about a 2-5% weight loss after 12 months.

The figure below shows the last 52 weeks of IMS prescription data trends for phentermine, Belviq, Qsymia and Xenical. Note that although the uptake rates appear rather robust, Qsymia is still only doing about 10,000 scripts per week (plotted on the left Y-axis) and on an annualized run rate of $36 million ($9 million reported by Vivus in Q1). Interestingly, despite years of flat prescription volume for phentermine, note the very recent pickup in volumes. It is plotted on the right Y axis and has grown from 133,000 prescriptions per week to now close to 137,000. Our guess is that this is coming from off-label combination use with Belviq.

Figure 8: Qsymia and Belviq volumes are still low but climbing



Source: IMS

Figure 9: Current obesity drugs and surgical approaches and approximate weight loss from various clinical trials

Non-Surgical Approaches: Modest Placebo-Adjusted Weight Loss Efficacy			
			
Xenical®	**Phentermine**	**Qsymia®**	**Belviq®**
2-5% over 12 months	3.8-4.4% over 6 months	6.6-8.6% over 12 months	3-3.3% over 12 months

Surgical Approaches: Substantial Efficacy, High Risk, Long-Term Complications				
Adjustable Gastric Banding (AGB) or LapBand®	**Vertical Banded Gastroplasty**	**Roux-en-Y Bypass**	**Biliopancreatic Diversion (BPD)**	**Sleeve Gastrectomy**
~20%	20-25%	25-30%	30-35%	25-35%

Source: Company Presentation

A table that further describes some of the attributes of the current drugs used for obesity treatment can be seen in Figure 10, which was recently published in the online version of the Journal Clinical Pharmacology & Therapeutics.

Figure 10: Attributes of currently used drugs for obesity

Mechanism of action	Drug	Effects and safety concerns	Efficacy	Status
Appetite suppressant. Stimulates anorexic signaling in hypothalamus or dopamine receptor in the hippocampus. Sympathomimetic agent similar to norepinephrine with central nervous system stimulatory activity	Phentermine	Appetite suppression and weight loss Side effects include dizziness, dry mouth, difficulty in sleeping, irritability, nausea, vomiting, diarrhea, or constipation. This drug has withdrawal symptoms	Weight loss greater than placebo was 3.6 kg (CI: 0.6–6.0 kg)	Approved by the FDA in 1959
	Amphetamine	Anorexia and weight loss Side effects include nervousness, restlessness, excitability, dizziness, headache, fear, anxiety, and tremor. Blood pressure and heart rate may increase. Chronic use may lead to dependence. These drugs have withdrawal symptoms	Weight loss greater than placebo was <1 kg (CI: 0.5–1.6 kg)	Off-label usage; approved for attention-deficit hyperactivity disorder
Serotonin, dopamine, and norepinephrine reuptake inhibitor that potentiates the neurotransmitter activity in the central nervous system	Lorcaserin (Belviq)	Limited weight-loss efficacy and possible increase in cancer risk Side effects include headache, infection, sinusitis, nausea, depression, anxiety, and suicidal thoughts. Possible concerns of cancer risk	Mean body weight loss: lorcaserin 5.8 ± 0.2 kg; placebo 2.2 ± 0.1 kg	Approved by the FDA in 2012
	Desvenlafaxine (Pristiq)	Anorexia, but effect on body weight is unclear Vision problems, headache, low libido, dry mouth, dizziness, insomnia, taste problems, vomiting, anxiety, sexual dysfunction, depression, high blood pressure, stomach ache, numbness and tingling, fatigue, and involuntary quivering	Mean body weight loss greater than placebo was 0.22–1.41 kg	Off-label usage; approved for depression
	Sibutramine (Meridia)	Limited weight-loss efficacy Increased risk for cardiovascular events and stroke		Approved by the FDA approval in 1997 but withdrawn in 2010 due to cardiovascular effects
Inhibits the neuronal uptake of dopamine, norepinephrine, and serotonin	Bupropion (Wellbutrin, Zyban)	Modest weight loss Nausea, vomiting, dry mouth, headache, constipation, increased sweating, joint aches, sore throat, blurred vision, strange taste in the mouth, agitation and insomnia, tremor, or dizziness may occur. Rare side effects include cardiovascular effects, hearing problems, severe headache, an increase in suicide risk, and respiratory problems	%Weight loss greater than placebo: bupropion SR 400 mg/day 5.1% (CI: 6.9–3.2%); bupropion SR 300 mg/day 2.2% (CI; 4.0–0.4%)	Off-label usage; approved for depression
Reversible inhibitor of intestinal lipases	Orlistat (Xenical)	Weight loss Increased number of bowel movements and potential changes in the bowel function and microbiota	Mean body weight loss greater than placebo was 4.2 kg	Approved by the FDA in 1999
Enhancing GABA signaling to promote anorexigenic signaling. Inhibiting voltage-gated channels and AMPA receptor in the orexigenic neurons	Topiramate (Topamax)	Appetite suppression and weight loss Fatigue, drowsiness, dizziness, loss of coordination, tingling of the hands/feet, bad taste in the mouth, and diarrhea. Mental problems such as confusion, slowed thinking, trouble concentrating or paying attention, nervousness, memory problems, or speech/language problems may also occur. Rare side effects include kidney stones, depression, suicidal thoughts/attempts, and vision loss	Weight loss greater than placebo was 6.5 kg (CI: 4.8–8.3 kg)	Off-label usage; approved for epilepsy
GLP-1 receptor agonist	Exenatide (Byetta, Bydureon)	Decreased blood glucose level and body weight Side effects include gastrointestinal symptoms, acute pancreatitis, dizziness, and headache. It might increase risks of sulfonylurea-induced hypoglycemia and thyroid cancer	Mean body weight change: exenatide −(2.49 ± 0.66) kg, placebo +(0.43 ± 0.63) kg	Off-label usage; approved for diabetes
	Liraglutide (Victoza)	Maintained normal blood glucose and body weight Increased risks of C-cell carcinoma and thyroid C-cell focal hyperplasia were observed in rats and mice	Weight loss greater than placebo was 4.4 kg (CI: 2.9–6.0 kg)	Off-label usage; approved for diabetes
Amylin analog	Pramlintide (Symlin)	Decreased blood glucose level and body weight Side effects include nausea, hypoglycemia, vomiting, headache, abdominal pain, and fatigue	%Weight loss greater than placebo was 2.2 ± 0.7%	Off-label usage; approved for diabetes
Cocktail drug	Phentermine/ topiramate (Osymia)	See above effects from individual drugs	%Weight loss from baseline was placebo −2.2%, (PHEN 7.5 mg/ TPM 46 mg) CR −9.3%, and (PHEN 15 mg/TPM 92 mg) CR −10.7%	Approved by the FDA in 2012

The various shades (low, medium, and high) represent FDA approval status and off-label usage of drugs.

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; CI, confidence interval; CR, controlled release; FDA, US Food and Drug Administration; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide 1; PHEN, phentermine; SR, sustained release; TPM, topiramate.

Source: Clinical Pharmacology & Therapeutics; VOLUME 95; NUMBER 1; January 2014
http://www.nature.com/clpt/journal/v95/n1/full/clpt2013204a.html

OBESITY DRUGS IN DEVELOPMENT

In the course of looking for possible competitors in development for obesity, we cobbled together a list of drugs with differing mechanisms of action from several different companies, but the only one that we found that looks like it might even be able to come close to beloranib is RM-493 from Rhythm. The table in Figure 11 on page 17 lists the drugs in development from various different sources, but our punchline is that most are either very early in development, been terminated, or have very low prospects.

Our comments on a few select products:

1. Merck's **MK-0493** is a novel and potent and selective agonist of the melanocortin receptor 4 (MC4R), which is one of the best validated genetic targets for obesity. It completed Phase 2 in 2006 and the results were published in 2009. However, it did not show significant weight loss and was limited by nausea and vomiting at the higher doses. Merck also reported increases in blood pressure in animal studies. In the 2009 publication, the authors concluded that *"agonism of MC4R is not likely to represent a viable approach to the development of antiobesity therapeutics"*

Citation: Clinical Pharmacology & Therapeutics 86, 659-666 (December 2009).
Weblink: http://www.nature.com/clpt/journal/v86/n6/full/clpt2009167a.html

2. Rhythm's **RM-493**, has a similar mechanism. It binds and activates the MC4R receptor in the paraventricular nucleus. In addition, it is a peptide, not a small molecule (and hence a subcutaneous injection) that was licensed from Ipsen and has shown "*promising preclinical results in obese primates…in June 2010*". *"Obese primates treated for 8 weeks lost an average of 13.5% of their body weight, with significant improvement in both insulin sensitivity and cardiovascular function"*. According to clinicaltrials.gov, a Phase 2 study in healthy obese subjects is due to read out in July of 2014. It is being tested as a once- and a twice-daily subcutaneous injection, with the primary efficacy endpoint being percent weight loss at 12 weeks. The pK effects of the drug as well as ambulatory blood pressure monitoring are listed as secondary outcome measures.

Weblink citations: http://www.medscape.com/viewarticle/746807_5
http://www.nature.com/clpt/journal/v95/n1/full/clpt2013204a.html
http://clinicaltrials.gov/ct2/show/NCT02041195?term=rm-493&rank=2

3. Merck's **MK-0557**, is an antagonist of the neuropeptide Y5 receptor. It finished a large Phase 3 study in 1,661 patients in 2005. However, it failed to induce any clinically meaningful weight loss after 52 weeks of treatment. Drug patients lost an average of 7.5 pounds while placebo patients lost an average of 4 pounds. The authors of the paper published in October 2006 in Cell Metabolism concluded that although the drug was not effective as monotherapy, it could perhaps be used in combination therapy. This basically ended a huge 10-year long obesity program for Merck and since neither of the two Merck drugs show up in the company's latest pipeline chart, we assume Merck has no active obesity programs.

Weblink citations: http://clinicaltrials.gov/ct2/results?term=mk-0557&Search=Search
http://www.nature.com/clpt/journal/v95/n1/full/clpt2013204a.html
http://www.merck.com/research/pipeline/home.html
http://www.sciencedaily.com/releases/2006/10/061003191604.htm

4. Shionogi's **velneperit**, has the same mechanism of MK-0557, which is a Y5 receptor inhibitor. It completed two Phase 2s in the US in February 2009 in a total of 1,566 obese patients. In one Phase 2, it showed that after one year, 35% of patients lost more than 5% of their weight compared to only 12% of placebo patients (P<0.0001). However this was only in the group that took the once-daily 800mg dose in combination with a reduced calorie diet. In addition, and most importantly, the drug group lost only 3.9% of weight after 54 weeks compared to 0.9% for the placebo group – for a placebo-subtracted difference of only 3% (p<0.0001). This is about the same efficacy that Belviq has shown in its clinical trials. In the second Phase 2, the drug group showed 6.9% weight loss at 60 weeks compared to placebo at 4.4% – for a placebo subtracted difference of only 2.5% (P<0.0002). Although it seems like a backup compound (S-237648) is in Phase 1 in Japan, we cannot find any evidence of Phase 3 trials in the US, and our guess is that the company concluded that it was not potent enough to be a commercially viable player against the current competition, and would be significantly behind Contrave, Belviq, and Qsymia. It is not currently listed on the company's pipeline chart that was updated on May 9, 2014 – but was still listed as being in Phase 2b in Japan only in February 2013.

Weblink citations: http://www.drugs.com/clinical_trials/shionogi-announces-positive-top-line-efficacy-results-year-long-studies-velneperit-novel-npy-y5-6742.html
http://www.shionogi.co.jp/en/ir/library/materials.html

It is widely recognized that the FDA very carefully and conservatively reviews the risk/benefit profile of all new weight loss drugs in development. While drugs must prove that they are effective by inducing clinically meaningful weight loss to FDA standards, they must also show very clean safety and tolerability profiles. The FDA came under heavy criticism in the late 1990s for allowing the approval of Redux (dexfenfluramine), which was eventually found to cause heart valve damage and even death in patients. Redux was part of the notorious Fen-Phen combination (Redux + phentermine) that was very popular and widely used in the mid-1990s due to strong weight loss, often over 10%. The FDA was also very conservative and strict in reviewing Sanofi-Aventis' drug Rimonabant in the mid-2000s, which never made it to market in the US. Rimonabant was a first-in-class endocannabinoid drug which was approved in Europe, and was eventually recalled in Europe due to these same issues. There have been numerous recent Advisory Panels on the topic of obesity drugs and, as referenced above, Orexigen was the only recent drug forced to do a cardiovascular outcomes trial prior to approval; now that the trial has been successfully completed, Orexigen should see a final approval in September.

The standards by which a drug proves clinically meaningful weight loss are very clear. The drug must induces 5% mean placebo-adjusted weight loss **OR** induce 5% body weight loss in at least 35% of drug patients (which must be about double the rate for placebo). Drugs technically need to meet only one of these hurdles to show approvable efficacy. FDA standards for safety are equally as rigid as evidenced by the lengthy CVOT trial required for Contrave. Additionally, the FDA requires that Phase 3 pivotal trials include at least 1,500 randomized to drug for one year of therapy in order to establish a large enough amount of safety data to ensure adequate review and analysis. Due to the orphan indications Zafgen is pursuing, the agency is making exceptions on the number of patients needed – but not the one-year safety timeframe.

Figure 11: Anti-obesity medications under development

Target	Drug	Company	Mechanism of action	Status	Comments
GLP-1 Receptor					
	Victoza	Novo Nordisk	GLP-1R agonist, GLP-1 mimicking	NDA Submission	FDA AdCom Sept 11 2014
	GSK-2374697	GlaxoSmithKline		Phase I	
Glucagon Receptor	ZP2929	Zealand Pharma		Phase I	
	ZYD1	Zydus Cadila		Phase I	
	Byetta (Exenatide)	Amylin	GLP-1R agonist, GLP-1 mimicking	Phase III	DEAD?/Not on AZ Pipeline
OXM Receptor					
	Oxyntomodulin	Prolor	GLP-1R agonist, OXM mimicking	Phase I Recruiting	
	TKS1225	Thiakis/Wyeth/Pfizer	GLP-1R agonist, OXM mimicking	Phase I	
Norepinephrine Reuptake/Transporter; Dopamine Reuptake					
Opioid Receptors	Contrave	Orexigen Therapeutics	Norepinephrine/dopamine reuptake inhibitor	NDA Submission	PDUFA date Sept 11, 2014
Sodium and Calcium Channels	Empatic	Orexigen Therapeutics		Phase II	Phase III on hold
Methionine aminopeptidase 2 (MetAP2)					
	Beloranib	Zafgen		Starting Phase III PW; P2 Complete in Severe obesity	
	ZGN-433	Zafgen		Phase I	
Melanocortin (MC) Receptors					
Insulin Receptor	RM-493	Rhythm Pharmaceuticals	Selective MC4R agonist, increases MC3R/4R signaling	Phase II	Results in August 2014
	MK-0493	Merck	Selective MC4R agonist, increases MC3R/4R signaling	Phase II Completed	DEAD
Neuropeptide Y (NPY)/ Peptide YY (PYY) Receptors	Obinepitide (TM30338)	7TM Pharma		Phase II	started in 2007; little evidence of company's existen
	MK-0557	Merck	Y5 receptor antagonist, NPY blocker	Phase II Completed	DEAD
	Velneperit (S-2367)	Shionogi USA	Y5 receptor antagonist, NPY blocker	Phase II Completed	DEAD
Cannabinoid-1 (CB1) Receptor	TM38837	7TM Pharma		Phase I Completed	in 2010, little evidence of company's existence
TGR5 (GPBAR1)	Sodium taurocholate	Satiogen Pharmaceuticals		Phase II	DEAD
Serotonin 5-HT3 Receptor	AD04 (ondanestron)	ADial Pharmaceuticals		Phase I	no active trials in obesity
Mitochondria; Prohibitin (PHB)	Adipotide	Arrowhead Research		Phase I	
Fibroblast Growth Factor Receptor (FGFR)	ISIS-FGFR4Rx	Isis Pharmaceuticals		Phase I	
Histamine H3 (HRH3) Receptor	HPP404	High Point Pharmaceuticals		Phase II	DEAD; P2 Terminated on clinicaltrials.gov
PP	PP1420	Wellcome Trust	Pancreatic polypeptide analog	Phase I Completed	
Amylin	Davalintide (AC2307)	Amylin	Amylin mimicking	Phase II	DEAD/not on AZ pipeline chart
Leptin	Metreleptin	Amylin/Takeda	Leptin receptor agonist	Approved Feb 2014	Very narrow indication in lipodystrophy
Pancreatic lipase	Cetilistat (ATL-962)	Alizyme/Takeda/Norgine	Pancreatic lipase inhibitor, inhibits intestinal lipid absorption	Approved in Japan	No US filing planned; Similar to Xenical

Source: BioMedTracker and Canaccord Genuity research

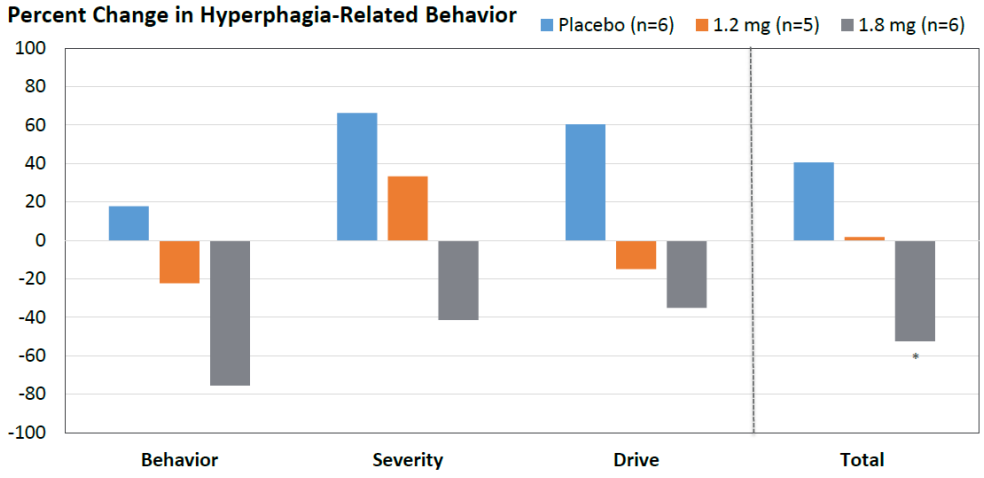
ZAFGEN'S THREE PROGRAMS

Prader-Willi Syndrome (PWS)

Prader-Willi syndrome (PWS) is a rare (~1 in 40,000 people in the US, according to PWS Association) disease that stems from improper functioning of the hypothalamus, resulting in hyperphagia and severe obesity, as well as debilitating behavioral and cognitive difficulties. Beloranib has been given orphan drug indication by the FDA in both the US and European Union, and has already demonstrated successful Phase 2a clinical trial results. Phase 3 trials are planned to begin later this year. The Phase 2a data is shown in the two figures below.

The Phase 3 program will involve two trials – one in Europe and one in the US with a total of 240 patients with BMI's >30kg/m2. It will involve two doses of 1.8mg and 2.4 mg and be placebo controlled for six months followed by a six-month safety extension component. Surprisingly, the FDA is going to allow the primary endpoints to be improvement in total body fat mass or hyperphagia-related behaviors, although secondary endpoints will certainly involve body weight, LDL, HDL, CRP, and others. We expect to see the six-month efficacy data in Q4 2015. Due to its orphan indication, we have modeled pricing for the drug at an annual per patient cost of $150,000.

Figure 12: Beloranib showed improvements in hyperphagia related behaviors in a Phase 2a trial in PWS patients

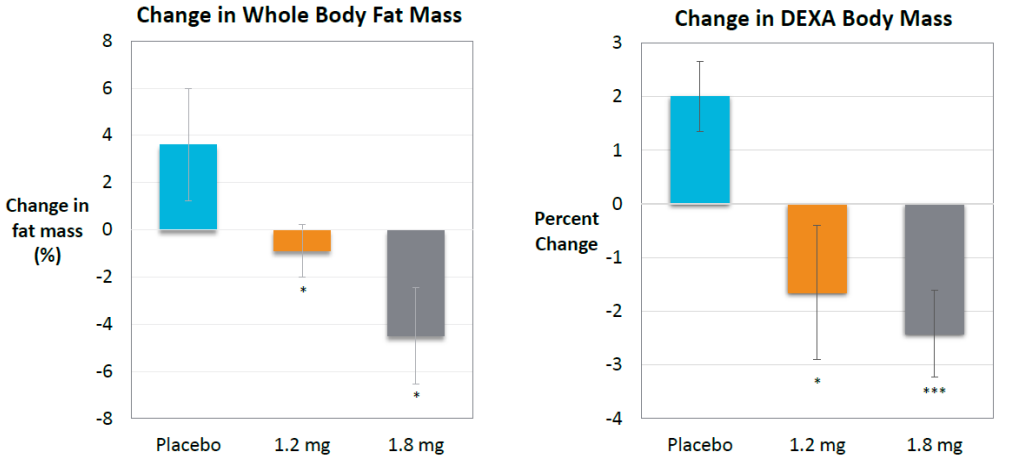


*, p<0.05

Reduction in behavior sub-scores were seen from baseline following randomized treatment with 1.8 mg beloranib

Source: Company presentation

Figure 13: Beloranib showed improvements in whole body fat mass and DEXA body mass in a Phase 2a trial in PWS patients



*, p<0.05; ***, p<0.005
Body composition and mass assessed by DEXA, dual-energy X-ray absorptiometry

Source: Company presentation

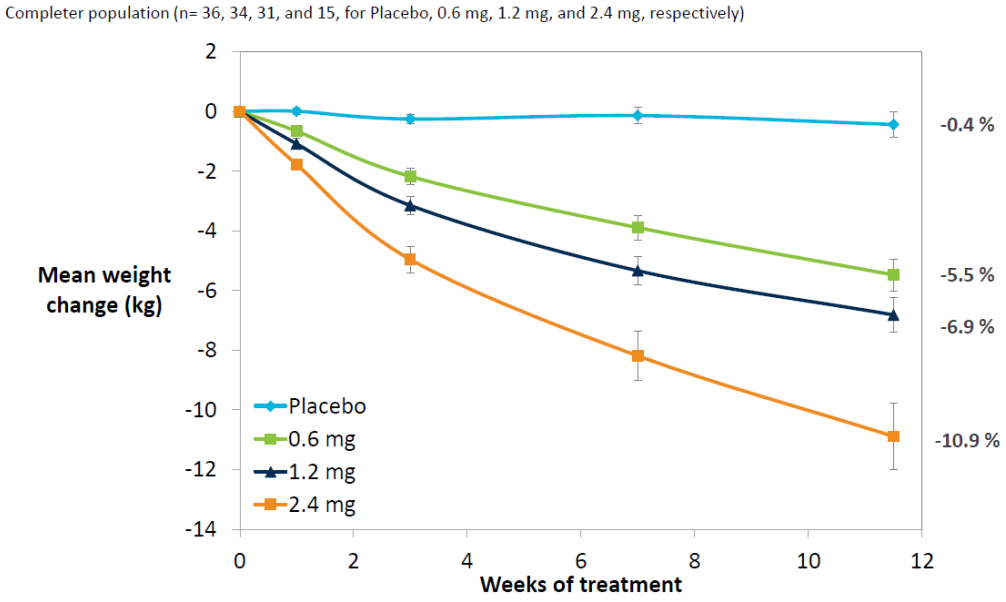
Craniopharyngioma

Craniopharyngioma is often viewed as a surgically-induced form of Prader-Willi syndrome. This arises when benign brain tumors near the pituitary gland and hypothalamus are excised, causing inevitable damage to these structures in the process. While the exact cause is different from that of PWS, the phenotype is more or less the same, and patients experience hyperphagia and severe obesity in much the same manner. Craniopharyngioma is also quite rare (~1 in 50,000 people in the US, according to Garnett et al.), for which the FDA has granted beloranib orphan drug indication for its treatment as well. We use the same pricing for the treatment of craniopharyngioma at $150,000 annually. Beloranib has not yet undergone clinical trials for the treatment of craniopharyngioma, but Zafgen intends to start Phase 2 in 14 patients soon, with results expected in Q1 2015, and likely followed immediately by Phase 3 trials in Q2 2015.

Severe obesity

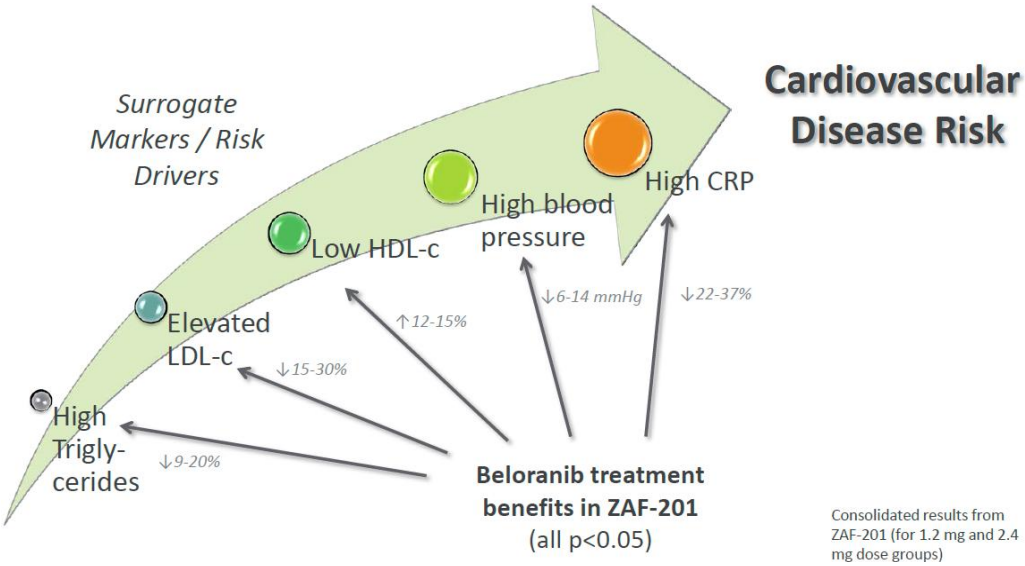
Zafgen has completed an impressive Phase 2a trial with beloranib in severe obesity in 160 patients. As shown in the figure below, beloranib presented an impressive 10.9% weight loss after only 12 weeks at the highest dose. And importantly, as shown in the figure below, it had equally impressive effects on several cardiovascular risk factors such as triglycerides, LDL, HDL, blood pressure and C-reactive protein. The next step is to conduct a Phase 2b study that will begin later this year in patients with BMI's up to 60 kg/m^2 with type 2 diabetes. The trial will have efficacy looks at both six and 12 months and we expect the first six-month efficacy look to come at the end of 2015. Zafgen also has a second-generation MetAP2i candidate under consideration for development in severe obesity and we assume this will be the compound that ultimately progresses into Phase 3.

Figure 14: Beloranib showed impressive weight loss in severely obese individuals after only 12 weeks



Source: Company presentation

Figure 15: Beloranib also showed impressive improvements in several cardiovascular risk markers in severely obese patients



Source: Company presentation

INTELLECTUAL PROPERTY

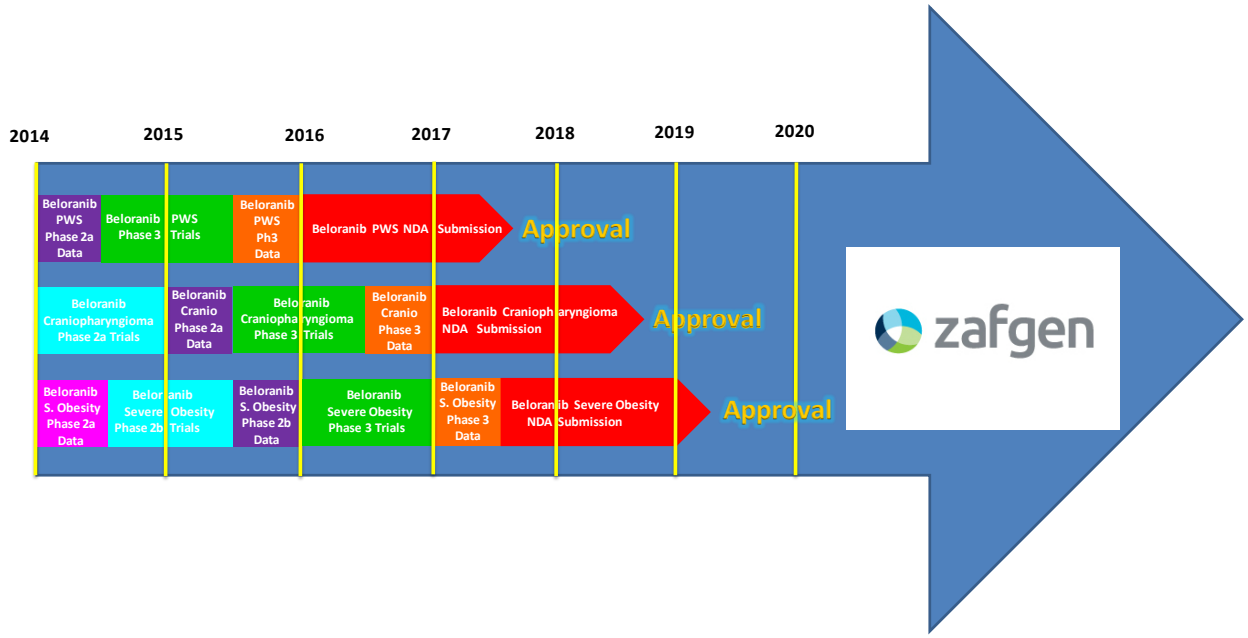
Figure 16: Zafgen already has two issued patents covering beloranib

Patent #	Name	IP Covered	Status	Expiration Date
8,642,650	Methods of treating an overweight or obese subject	Administering a MetAP2 inhibitor in which the amount administered does not substantially modulate angiogenesis.	Issued	2029
8,735,447	Crytalline solids of a MetAP-2 inhibitor and methods of making and using the same	Methods of making and using crystalline forms of 6-O-(4-dimethylaminoethoxy)cinnamoyl fumagillol and variants thereof.	Issued	2032

Source: Company reports and Canaccord Genuity estimates

TIMELINES FOR ZAFGEN

Figure 17: Timelines for the three main Zafgen programs predict launches in 2018, 2019, and 2020



Source: Company disclosures

MANAGEMENT TEAM

Figure 18: Zafgen key management members

Name	Title	Work History	Joined Zafgen in:
Thomas E. Hughes, Ph.D.	Chief Executive Officer	Novartis AG Miragen Therapeutics, Inc. Broadview Ventures Nimbus Discovery, LLC.	2008
Dennis D. Kim, M.D., M.B.A.	Chief Medical Officer	Orexigen Therapeutics EnteroMedics, Inc. Amylin Pharmaceuticals, Inc.	2011
James E. Vath, Ph.D.	Head of Discovery and Development	Phylogix, Inc. Praecis Pharmaceuticals Millennium Pharmaceuticals Genetics Institute	2006
Patricia Allen	Chief Financial Officer	Alnylam Pharmaceuticals Alkermes, Inc. Deloitte & Touche, LLP.	2013
Alicia Secor	Chief Commercial Officer	Synageva BioPharma Corp. Genzyme Biosurgical Specialties Alkermes Centocor Pfizer	2014

Source: Company reports

INVESTMENT RISKS

- Delays in any of its three main programs due to regulatory concerns or logistical hurdles.
- Failure of beloranib in the Prader-Willi Syndrome Phase 3 program (due Q4 2015), the Phase 2 craniopharyngioma program (due Q1 2015), or the severe obesity P2b program (due Q4 2015).
- Failure to ultimately obtain FDA approval for beloranib in one or more of the three indications.
- Unforeseen safety signals that pop up due to beloranib's not-fully-understood mechanism and pleiotropic effects that create the potential for off-target interactions leading to unpredictable side effects.
- Failure to properly manufacture a more commercially viable injection presentation than the form currently used in clinical trials.
- Failure to obtain additional funding to finish development and commercialize beloranib.

Figure 19: Zafgen balance sheet

(In millions)	Dec-12	Dec-13	Mar-14
ASSETS			
Current Assets:			
Cash & cash equivalents	9.9	35.5	38.5
Restricted cash			
Short-term investments			
Accounts receivables		1.6	1.2
Inventory			
Prepaid expenses & other current assets	0.4	0.2	0.3
Deferred offering costs			
Total Current Assets	10.3	37.4	39.9
Property, Plant, & Equipment, net	0.0	0.0	0.0
Goodwill			
Intangibles, net			
Other assets, net	0.6	0.7	1.4
TOTAL ASSETS	**11.0**	**38.1**	**41.3**
Working Capital			
LIABILITIES & STOCKHOLDERS EQUITY			
Current Liabilities			
Accounts Payable	1.2	2.0	1.0
Accrued expenses	1.7	0.9	1.6
Notes payable, net of discount - related parties			0.5
Current portion of royalty interest obligation			
Current portion of deferred revenue			
Current portion of long-term debt			
Total current liabilities	2.9	2.9	3.1
Long-term Liabilities			
Related party debt, including accrued interest			
Other liabilities			6.9
Total Liabilities	2.9	2.9	9.9
Stockholders' Equity			
Preferred stock	62.8	103.8	104.3
Common stock	0.0	0.0	0.0
Additional paid-in capital	0.1	0.3	0.5
Accumulated deficit	(54.9)	(68.9)	(73.4)
Other			
Treasury Stock			
Total stockholders' equity	8.1	35.2	31.4
TOTAL LIABILITITES AND EQUITY	**11.0**	**38.1**	**41.3**

Source: Company reports and Canaccord Genuity estimates

Figure 20: Zafgen statement of cash flows

(In millions except per share amount)	Dec-12	Dec-13	Mar-14
	12 mo	12 mo	3 mo
CASH FLOWS FROM OPERATING ACTIVITIES			
Net income (loss)	(13.9)	(14.0)	(4.5)
Depreciation & Amortization	0.0	0.0	0.0
Other non-cash adjustments	0.2	0.6	0.1
Change in opearing assets & liabilities	0.1	(1.6)	0.3
Net Cash from Operations	**(13.6)**	**(15.0)**	**(4.0)**
CASH FLOWS FROM INVESTING ACTIVITIES			
Purchases of fixed assets, net	(0.0)	(0.0)	(0.0)
Purchase of short-term investments, net			
Payment of contingent consideration			
Acquisition of intangible assets, business and other invests.			
Net Cash from Investing	(0.0)	(0.0)	(0.0)
CASH FLOWS FROM FINANCING ACTIVITIES			
Proceeds from issuance of preferred stock	16.1	40.8	0.4
Proceeds from issuance of common stock and options excercises	0.0		
Purchase of treasury stock			
Payment of Long term debt principle			
Proceeds from convertible notes			7.4
Proceeds from secured promissory notes & credit facility	6.0		
Other credit/debt financing		(0.2)	(0.8)
Payoff of credit facility			
Financing Costs			
Net Cash from Financing	22.1	40.6	7.0
Foreign exchange rate effect			
Net Increase in Net Cash	**8.5**	**25.6**	**3.0**
Net Cash at beginning of year	1.5	9.9	35.5
Short term investments.			
Net Cash/Investments, End of Period	**9.9**	**35.5**	**38.5**

Source: Company reports and Canaccord Genuity estimates

Figure 21: Zafgen complete P&L

	Beloranib		Son of Bel	TOTAL REVS	COGS	Gross Profit	Margin % rev	R&D	% rev	SG&A	% rev	Total OPEX	Op Income	% rev	Other Total	Pretax Inc	% rev	GAAP Net Income	GAAP EPS (diluted)	Diluted shares
2012								11.5		2.2		13.8	(13.8)		(0.1)	(13.9)		(13.9)	**($3.11)**	4.5
1Q								2.6		0.9		3.5	(3.5)		(0.0)	(3.5)		(3.5)	**($0.77)**	4.6
2Q																				
3Q																				
4Q																				
2013								9.6		4.2		13.8	(13.8)		(0.2)	(14.0)		(14.0)	**($3.06)**	4.6
1Q								3.3		1.2		4.5	(4.5)		0.0	(4.5)		(4.5)	**($0.29)**	15.8
2QE								5.0		2.0		7.0	(7.0)		0.1	(6.9)		(6.9)	**($0.44)**	15.8
3QE								15.0		2.5		17.5	(17.5)		0.1	(17.4)		(17.4)	**($0.77)**	22.7
4QE								8.0		2.5		10.5	(10.5)		0.1	(10.4)		(10.4)	**($0.77)**	22.7
2014E								31.3		8.2		39.5	(39.5)		0.2	(39.3)		**(39.3)**	**($2.26)**	19.2
2015E								40.0		12.0		52.0	(52.0)		0.1	(51.9)		(51.9)	**($2.26)**	22.9
2016E								45.0		15.0		60.0	(60.0)		0.1	(59.9)		(59.9)	**($2.13)**	28.2
2017E								65.0		20.0		85.0	(85.0)		0.1	(84.9)		(84.9)	**($2.54)**	33.4
2018E	121.8			**121.8**	12.2	109.6	90.0%	100.0	82%	25.0	21%	137.2	(15.4)		0.1	(15.3)		(15.3)	**($0.40)**	38.8
2019E	260.8	104.3		**365.2**	36.5	328.7	90.0%	150.0	41%	50.0	14%	236.5	128.7	35.2%	0.1	128.7	35%	128.7	**$3.29**	39.2
2020E	307.3	167.6	194.4	**669.3**	66.9	602.4	90.0%	165.0	25%	200.0	30%	431.9	237.4	35.5%	0.1	237.5	35%	237.5	**$6.00**	39.6
2021E	359.0	203.5	416.5	**978.9**	97.9	881.0	90.0%	132.0	13%	250.0	26%	479.9	499.0	51.0%	0.1	499.1	51%	309.4	**$7.74**	40.0
2022E	416.6	243.5	669.0	**1,329.1**	132.9	1196.2	90.0%	118.8	9%	275.0	21%	526.7	802.4	60.4%	0.1	802.5	60%	497.5	**$12.33**	40.4
%Growth																				
1Q								24.4%		40.5%		28.4%	28.4%		-166.7%	27.3%		27.3%		245.4%
2QE																				
3QE																				
4QE																				
14E/13E								227.1%		95.4%		186.8%	186.8%		-182.2%	180.3%		180.3%		320.3%
15E/14E								27.9%		45.5%		31.6%	31.6%		-69.0%	32.1%		32.1%		19.2%
16E/15E								12.5%		25.0%		15.4%	15.4%		0.0%	15.4%		15.4%		22.8%
17E/16E								44.4%		33.3%		41.7%	41.7%		0.0%	41.7%		41.7%		18.8%
18E/17E								53.8%		25.0%		61.4%	-81.9%		0.0%	-81.9%		-81.9%		15.9%
19E/18E	114.2%			**199.9%**	199.9%	199.9%	0.0%	50.0%		100.0%		72.4%	-935.2%		0.0%	-939.1%		-939.1%		1.0%
20E/19E	17.8%	60.7%		**83.3%**	83.3%	83.3%	0.0%	10.0%		300.0%		82.6%	84.5%		0.0%	84.5%		84.5%	82.7%	1.0%
21E/20E	16.8%	21.4%	114.2%	**46.3%**	46.3%	46.3%	0.0%	-20.0%		25.0%		11.1%	110.2%		0.0%	110.2%		30.3%	29.0%	1.0%
22E/21E	16.0%	19.7%	60.7%	**35.8%**	35.8%	35.8%	0.0%	-10.0%		10.0%		9.8%	60.8%		0.0%	60.8%		60.8%	59.2%	1.0%

Source: Company reports and Canaccord Genuity estimates

Figure 22: Zafgen summary P&L

Year End: December 31	2012	2013	1Q14	2Q14E	3Q14E	4Q14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Beloranib										$0.0	$121.8	$365.2	$474.9	$562.5	$660.1
Total Revenue										**$0.0**	**$121.8**	**$365.2**	**$669.3**	**$978.9**	**$1,329.1**
Gross Profit										$0.0	$109.6	$328.7	$602.4	$881.0	$1,196.2
Gross Margin										*0.0%*	*90.0%*	*90.0%*	*90.0%*	*90.0%*	*90.0%*
SG&A	$2.2	$4.2	$1.2	$2.0	$2.5	$2.5	$8.2	$12.0	$15.0	$20.0	$25.0	$50.0	$200.0	$250.0	$275.0
R&D	$11.54	$9.56	$3.28	$5.00	$15.00	$8.00	$31.28	$40.00	$45.00	$65.00	$100.00	$150.00	$165.00	$132.00	$118.80
Adj. Operating Income	**(13.8)**	**(13.8)**	**(4.5)**	**(7.0)**	**(17.5)**	**(10.5)**	**(39.5)**	**(52.0)**	**(60.0)**	**(85.0)**	**(15.4)**	**128.7**	**237.4**	**499.0**	**802.4**
Adj. Operating Margin												*35.2%*	*35.5%*	*51.0%*	*60.4%*
Non-Op	(0.1)	(0.2)	0.0	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Tax Rate														38.0%	38.0%
GAAP Net Income	(13.9)	(14.0)	(4.5)	(6.9)	(17.4)	(10.4)	(39.3)	(51.9)	(59.9)	(84.9)	(15.3)	128.7	237.5	309.4	497.5
Adj. Net Income	(13.8)	(13.6)	(4.5)	(6.9)	(17.4)	(10.4)	(39.3)	(51.9)	(59.9)	(84.9)	(15.3)	128.7	237.5	309.4	497.5
Net Margin												*35.2%*	*35.5%*	*31.6%*	*37.4%*
GAAP EPS (diluted)	($3.11)	($3.06)	($0.29)	($0.44)	($0.77)	($0.77)	($2.26)	($2.26)	($2.13)	($2.54)	($0.40)	$3.29	$6.00	$7.74	$12.33
Adjusted EPS (diluted)	**($3.09)**	**($2.98)**	**($0.29)**	**($0.44)**	**($0.77)**	**($0.77)**	**($2.26)**	**($2.26)**	**($2.13)**	**($2.54)**	**($0.40)**	**$3.29**	**$6.00**	**$7.74**	**$12.33**
Diluted Shares (M)	4.5	4.6	15.8	15.8	22.7	22.7	19.2	22.9	28.2	33.4	38.8	39.2	39.6	40.0	40.4
Year-over-Year Growth															
Beloranib												200%	30%	18%	17%
Total Revenue												**200%**	**83%**	**46%**	**36%**
Gross Profit											*0%*	*200%*	83%	46%	36%
SG&A			*40%*	*0%*	*28%*	*0%*	*95%*	*46%*	*25%*	*33%*	*25%*	*100%*	300%	25%	10%
R&D			*24%*	*0%*	*40%*	*0%*	*227%*	*28%*	*13%*	*44%*	*54%*	*50%*	10%	-20%	-10%
Operating Income													85%	110%	61%
Net Income													84%	30%	61%
Adj. EPS													***83%***	***29%***	***59%***

Source: Company reports, Canaccord Genuity Inc. estimates

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	984	100.0%	

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Zafgen	1A, 2, 3, 5, 7

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