Zafgen Buy Pitch (NASDAQ: ZFGN)

Undervalued Growth Potential in the Obesity Market

Thesis

ZFGN is a Long Term BUY

- Undervalued Growth Potential in the Obesity Market
  - Likely to achieve first-to-market status for beloranib in orphan obesity diseases (PWS and HIAO)
  - Superior efficacy in the orphan disease market will serve as proof of concept for early-stage general obesity treatments in pipeline--opportunity to enter the high growth obesity market
- Misunderstood Change in PWS Phase III Primary Endpoints
- Experienced Management Team & Strong Institutional Backing
- Attractive M&A Target
  - Unpartnered company with late-stage drug candidates
    - Ex-US, ex-EU commercialization opportunity for PWS & HIAO
  - Opportunity for cost synergies (high op-ex)

Current Price*: $32.60

Target Price: $46.05

Upside: 41%

*As of 5/21/2015

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I. Background and Overview

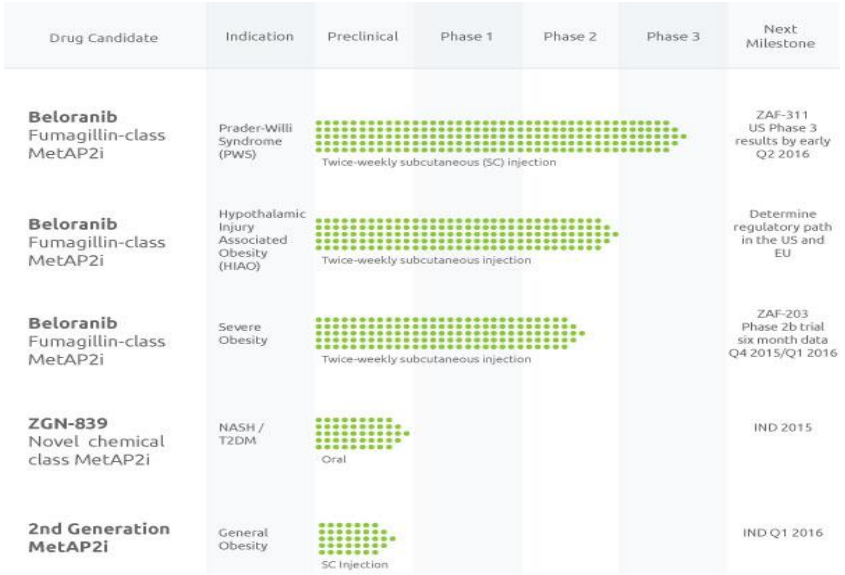
ZFGN is developing first-in-class, first-to-market drugs in the orphan obesity market

Company Overview

- **Late-stage clinical biotechnology company with a focus on <u>obesity</u>**
  - Founded in 2005, IPO in 2014
  - Focusing on **orphan** drug development
- **Multiple late-stage trials**
  - PWS: Phase III
  - HIAO: Completed Phase IIb
  - Severe Obesity: Phase IIb
- **Preclinical candidates with large target markets**
  - ZGN-839: NASH/T2DM
  - 2nd Generation MetAP2i: General Obesity

Financial Profile

Market Cap ($M)	283
Price	$32.60
52-week Range	16.01-55.36
Total Cash & Equiv ($mm)	234.2
Price to Book	3.95



Sources: Company filings, Bloomberg, Zafgen Website

I. Background and Overview

ZFGN is supported by a strong, experienced management team and VC backing

Management Team

Thomas E. Hughes, Ph.D
CEO

- 25 years of R&D experience
- Oversaw development of vildagliptin at Novartis

Patrick Loustau
President

- 20 years of biopharmaceutical management experience
- $10.7B P&L

Patricia Allen
CFO

- 20 years of financial leadership experience in biotech industry
- Influential in Alnylam capital financing

Alicia Secor
CCO

- 20+ years of commercial development experience
- Recently VP of Metabolic Diseases at Genzyme

James E. Vath, Ph.D.
Head of Discovery and Development

- 20+ years of pharmaceutical and biotechnology experience
- Multiple IND filings and a product approval

Dennis D. Kim, M.D., M.B.A.
CMO

- Endocrinologist with 10 years experience in biotech
- Obesity business development experience

Strong Backing from VCs

RA Capital Advisors

THIRD ROCK VENTURES

AltaPartners

venrock

Sources: Company filings, Zafgen Website

I. Background and Overview

There are many benefits to ZFGN's strategy of entering the obesity market through orphan indications

Benefits of Orphan Drug Development

- **Market exclusivity**
  - **7 years** in US, **10 years** in EU
- **Reduced R&D costs (US)**
  - **50% tax credit** on R&D cost
  - R&D grants for Phase I-III trials
  - Fee waivers (PDUFA)
- **Lower potential for competition**
- **High pricing power**
  - Small population with high unmet need translates to flexible pricing
- **Expedited FDA approval process**
  - 10 months vs. 13 months for non-orphan drugs

Using Orphan Indications to Enter the General Obesity Market

- **Beloranib trials can be used as proof of concept for the MOA**
  - Cheaper, smaller-scale trials to prove superior efficacy
- **2nd gen oral treatment with shared MOA in development for NASH and type 2 diabetes**
  - IND mid-2015
- **Familiarize physicians with product lines**
  - Quicker adoption of future general obesity drugs
  - Less operating costs for marketing → higher profitability

Sources: EvaluatePharma™ Orphan Drug Report 2014, BioMedTracker Orphan Drugs 2013

I. Background and Overview

PWS and HIAO have small patient populations but provide the opportunity for pricing power and expansion into general obesity.

Prader-Willi Syndrome (PWS)

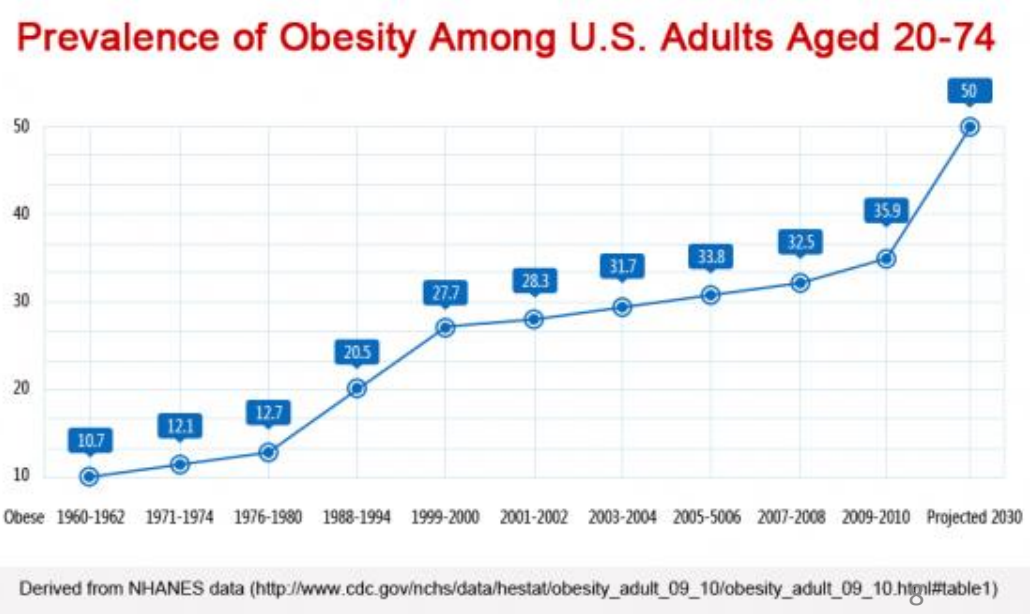
- Insatiable appetite causes obesity and associated complications
- Prevalence: 1/15,000 – 1/30,000

Hypothalamic Injury-Associated Obesity (HIAO)

- Impaired hypothamic regulation of hormone levels can cause obesity
- Prevalence: 1/50,000

Severe Obesity

- Demographic trends make the obesity market increasingly attractive
- US obese population: **200+ million**
- US market size: **$5.3 billion**
- Market CAGR to 2019: **39.45%**

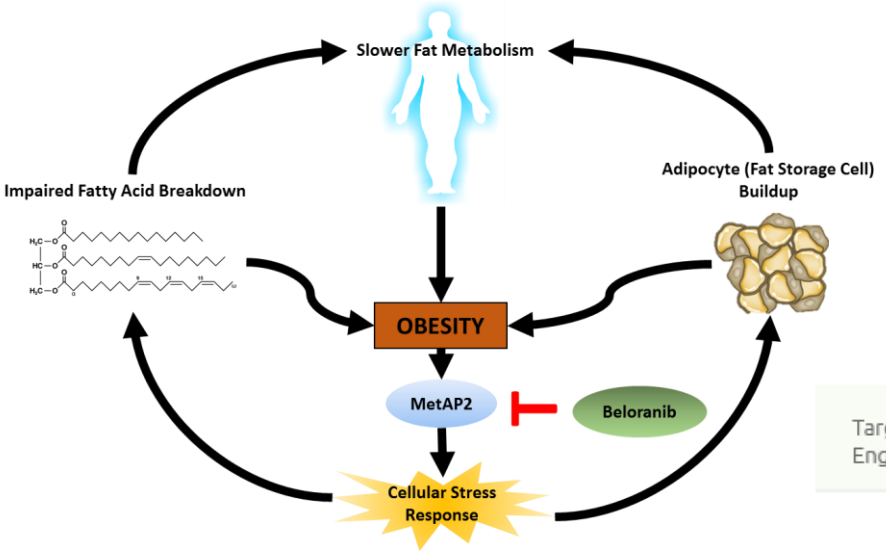


Sources: TechNavio Global Anti-Obesity Drugs Market 2015-2019

I. Background and Overview

ZFGN leads the development of treatment for orphan obesity-related diseases with beloranib, a first-in-class MetAP2 inhibitor

Beloranib Mechanism of Action: Inhibiting MetAP2



Competitive Landscape (PWS and HIAO)

- Ferring Pharmaceuticals: Phase II, PWS
- Essentialis, Inc.: Phase II, PWS
- Rhythm Pharmaceuticals: Phase I

Target Engagement	Pathway Impact	Drug Effect(s)	Disease Impact
MetAP2 Inhibition	Attenuated ERK Phosphorylation + Attenuated Cellular Stress Cascade + Gene Expression Changes for SREBP and ROR Pathways + Metabolite and Hormonal Changes	Reduced Hunger and Food Intake Reduced Fat Synthesis Increased Fat Burning Reduced Cholesterol Synthesis Reduced Inflammation	Rapid Weight Loss Improved Glycemic Control Reduced LDLc and CRP --> Reduced Cardiovascular Risk Improved Liver Health

Sources: Zafgen Financial Reports

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II. Beloranib: PWS Indication

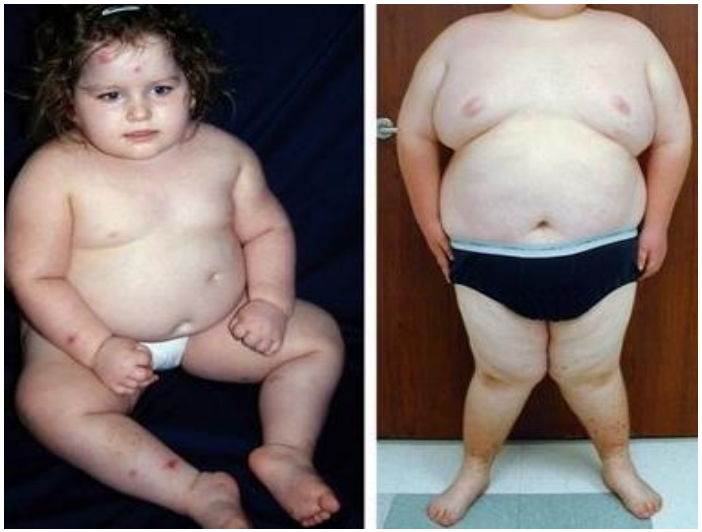
Prader-Willi Syndrome is a genetic disease that causes insatiable hunger, leading to obesity related complications: *there are currently no treatments that curb hunger and promote weight loss in patients*

PWS Diagnosed Market Overview

- US: ~8,500-9,000 patients
- EU: ~13,000-14,000 patients
- Diagnosed through genetic screen

PWS Pathology

- Uncontrollable hunger and obesity
- Physical and mental development issues
- Annual treatment cost ~$100,000



Treatment	Goal	Difficulties
Strict Dietary Supervision	Reduce caloric intake and prevent weight gain	Labor intensive enforcement • Locking cabinets/refrigerators • Constant monitoring
Behavioral Therapy	Mitigate compulsive food seeking behavior	• Variations in quality of care • Highly variable efficacy
Growth Hormones	Increase stature and lean muscle formation	• Increased risk for cancer and diabetes • Does not reduce hunger
Beloranib	Promote weight loss and curb hyperphagia (hunger)	• 2x weekly subcutaneous injections

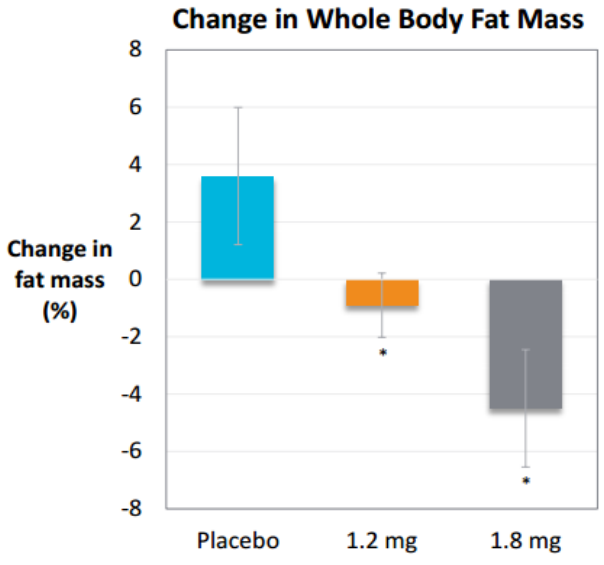
Source: Eunice Kennedy Shriver National Institute of Child Health and Human Development

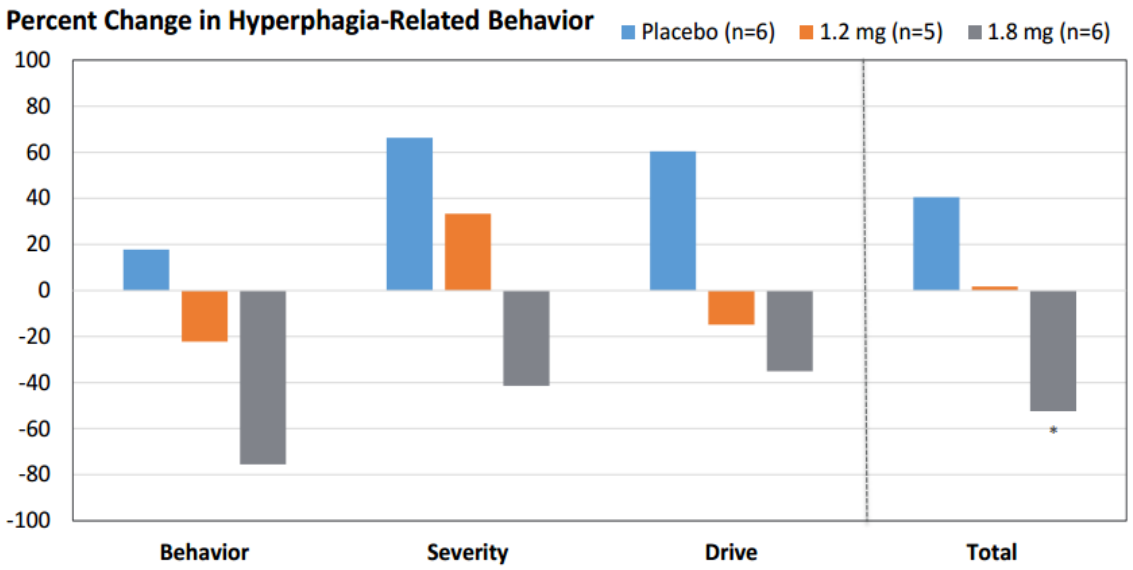
II. Beloranib: PWS Indication

Clinical trial data indicates that beloranib can reduce weight and hunger significantly

"The biggest problem in Prader-Willi patients is the incessant drive to eat and there's currently nothing on the market to address that. If beloranib's results are replicable in phase III, I don't see why it won't be used for all [Prader – Willi] patients."

- Dr. Robert Nicholls, Ph.D, Children's Hospital of Pittsburgh





Zafgen has initiated Phase III trials for beloranib in PWS that are set to conclude in May 2016

- Primary endpoints
  - Changes in total body fat mass
  - Changes in hyperphagia – related behavior
- Secondary endpoints
  - Changes in LDL cholesterol
  - Changes in HDL cholesterol

Source: Zafgen Investor Presentation

II. Beloranib: PWS Indication

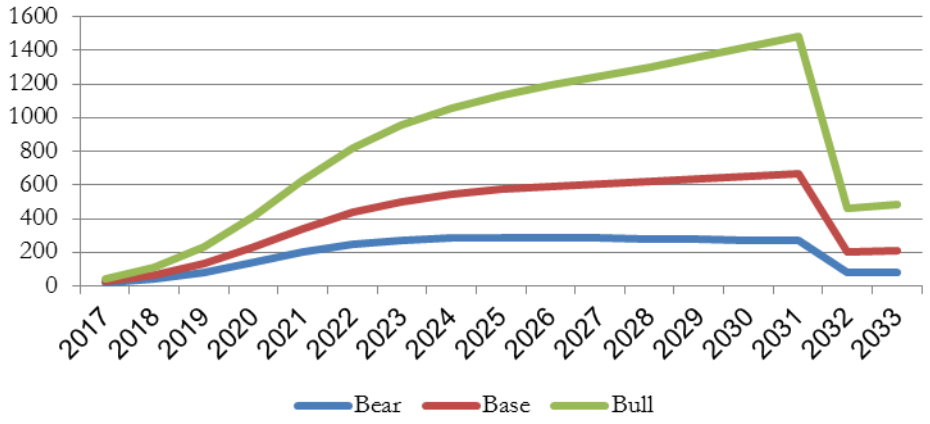
Once it reaches market, beloranib is uniquely poised to become widely adopted by the PWS population

- **Beloranib is a novel, first-in-class small molecule**
- **Orphan designation increases market penetration**
  - Potential patients will be clustered in more concentrated networks around hospitals or treatment centers
  - Federal exclusivity in US (7yrs) and EU (10yr)

Model Assumption	Bear	Base	Bull
U.S. Peak Penetration	25%	35%	45%
E.U. Peak Penetration	25%	30%	35%
Adult Approval Prob.	80%		
Pediatric Approval Prob.	75%		
Treatment Price U.S.	$90k	$110k	$150k
Treatment Price E.U.	$75k	$90k	$125k
Incidence	1 in 15,000		

- **No trial subjects dropped out due to adverse effects**
  - The drug promises to be well tolerated in the patient population
- **Subcutaneous injection delivery will not hinder patient uptake**
  - Blockbusters such as insulin are administered up to 3x/day
  - Beloranib's life-saving benefits in combating morbid obesity & hyperphagia outweigh inconvenience of injections

PWS Risk Adj. Revenue Projections (US & EU)



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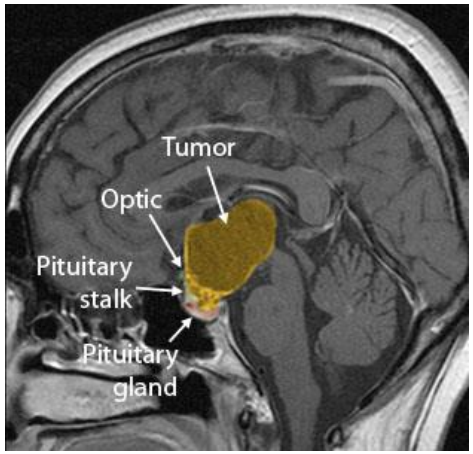
III. Beloranib: HIAO Indication

Hypothalamic injury associated obesity is a rare form of medically induced obesity caused by damage to the hypothalamus upon treatment on CNS tumors.

HIAO Market Overview

- **Incidence: 0.13 to 0.17 per 100,000**
  - 400-500 cases/year in the U.S.
  - 650-850 cases/year in the E.U.
- **Treatable Population: 50%**
  - About **half** of patients treated for hypothalamic injury develop hyperphagia and obesity



Current Methods of Treatment Demonstrate an Unmet Need

Treatment	Goal	Difficulties
Lifestyle changes	Caloric restriction, increased physical activity	Difficult to enforce, advice rather than treatment
Appetite suppressants	Inhibition of serotonin, dopamine, etc. to mitigate food seeking behavior	Benefits are unclear (insufficient testing), lack of sufficient efficacy data
CNS regulation	Suppression of insulin secretion (octreotide)	No guaranteed induction of weight loss
Hormone replacement	Treating adrenal insufficiency	Insufficient efficacy testing
Surgical treatment	Gastric bypass surgery to curb hyperinsulinemia	Intensive and lacks sufficient efficacy testing

Sources: UCLA, Columbia University College of Physicians & Surgeons

III. Beloranib: HIAO Indication

Belonarib treatment of HIAO resulted in rapid and significant weight loss and improvements in cardiometabolic biomarkers.

Compelling Phase II Results

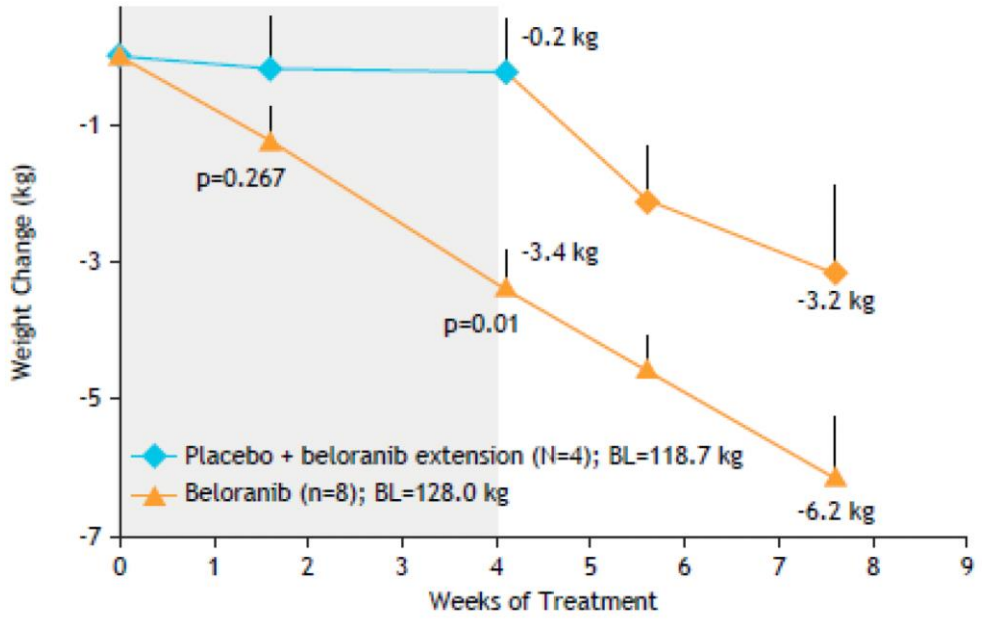
- Significant weight loss over four and eight week periods
- Reduction of cardiovascular risk factors including lipid parameters and markers of inflammation
- Very mild and transient adverse events

Patient Population Overview

Age (Years)	31.9
Mean BMI (kg/m^2)	42.9
Mean Body Weight (kg)	126.4

Change in Weight (4 wks.)
Belonarib: -3.40 ± 0.6 kg
Placebo: -0.25 ± 0.8 kg

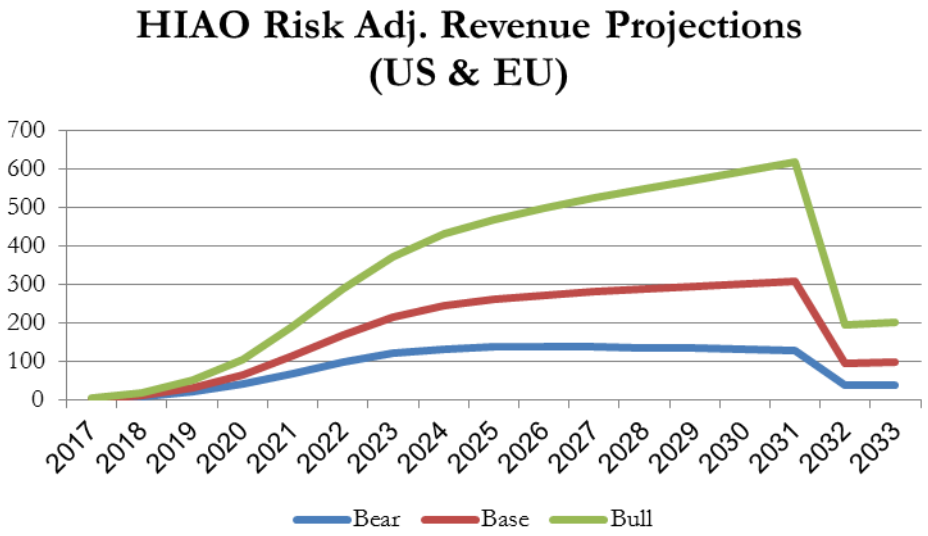
Exhibit 1: Mean Change in Body Weight over Time



Sources: Zafgen Company Website

III. Beloranib: HIAO Indication

We expect belonarib to succeed in the HIAO market due to first-to-market status and high efficacy.



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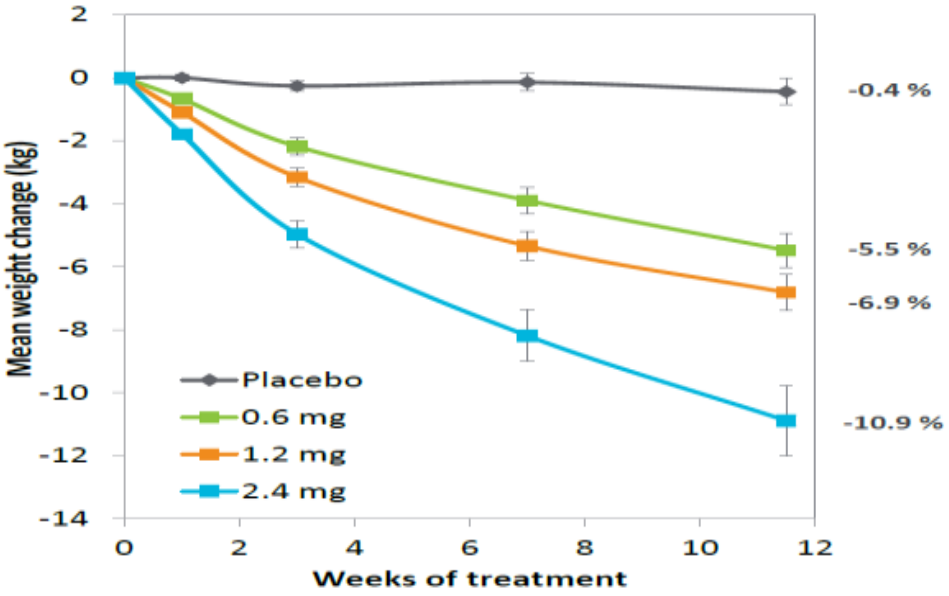
IV. Severe Obesity in T2 Diabetics

Beloranib's strong efficacy will allow it to cross over to the non-orphan obesity market

Phase 2a PoC 12 week study



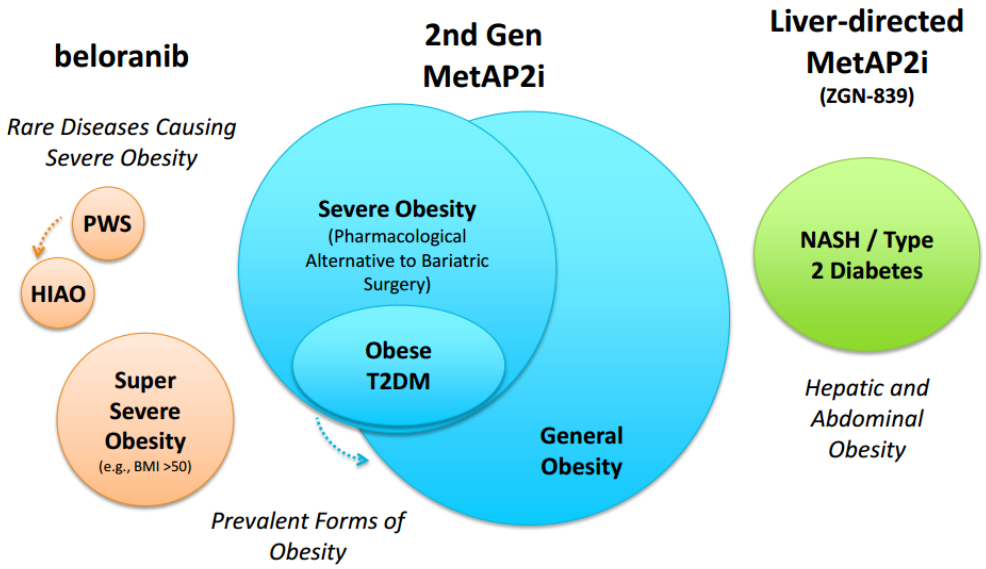
Treating Severe Obesity

- Best-in-class efficacy: 10.9kg. weight loss in 12 wks., no plateau of weight loss over time
- Clinically Significant Change in Secondary Endpoints:
  - Reduced cardiometabolic risk markers
  - Reduced sense of hunger
  - Reduction in LDL-cholesterol
  - Increase in HDL-cholesterol
  - Reduction in triglycerides
  - Reduction in blood pressure (12.0 mmHg)
- Targeting severe obesity in Type 2 diabetes for first obesity indication because of potential synergies due to MOA
- Beloranib for severe obesity – phase 2b six month data expected Q4 2015/Q1 2016
- General Obesity: 2nd Generation MetAP2i – IND Q1 2016

Sources: World Health Organization, Gallup

IV. Other Pipeline Drugs and Expansion Potential

MetAP2 inhibitors have vast physiological impacts and may have utility in the treatment of other metabolic diseases



Nonalcoholic Fatty Liver Disease

- Affects 20% of U.S. adults, 30% of worldwide developed country population
  - Prevalence could reach **50%** by **2030**
- Similar pre-clinical efficacy as Intercept but potential for better side effect profile and potentially improved efficacy in certain sub-populations

Nonalcoholic Steatohepatitis

- Prevalence of 3.5 – 5%
- Targeting unique sub-population of Type 2 Diabetics due to differentiated mechanism of action

Sources: World Health Organization, Gallup WebMD, Zafgen Website

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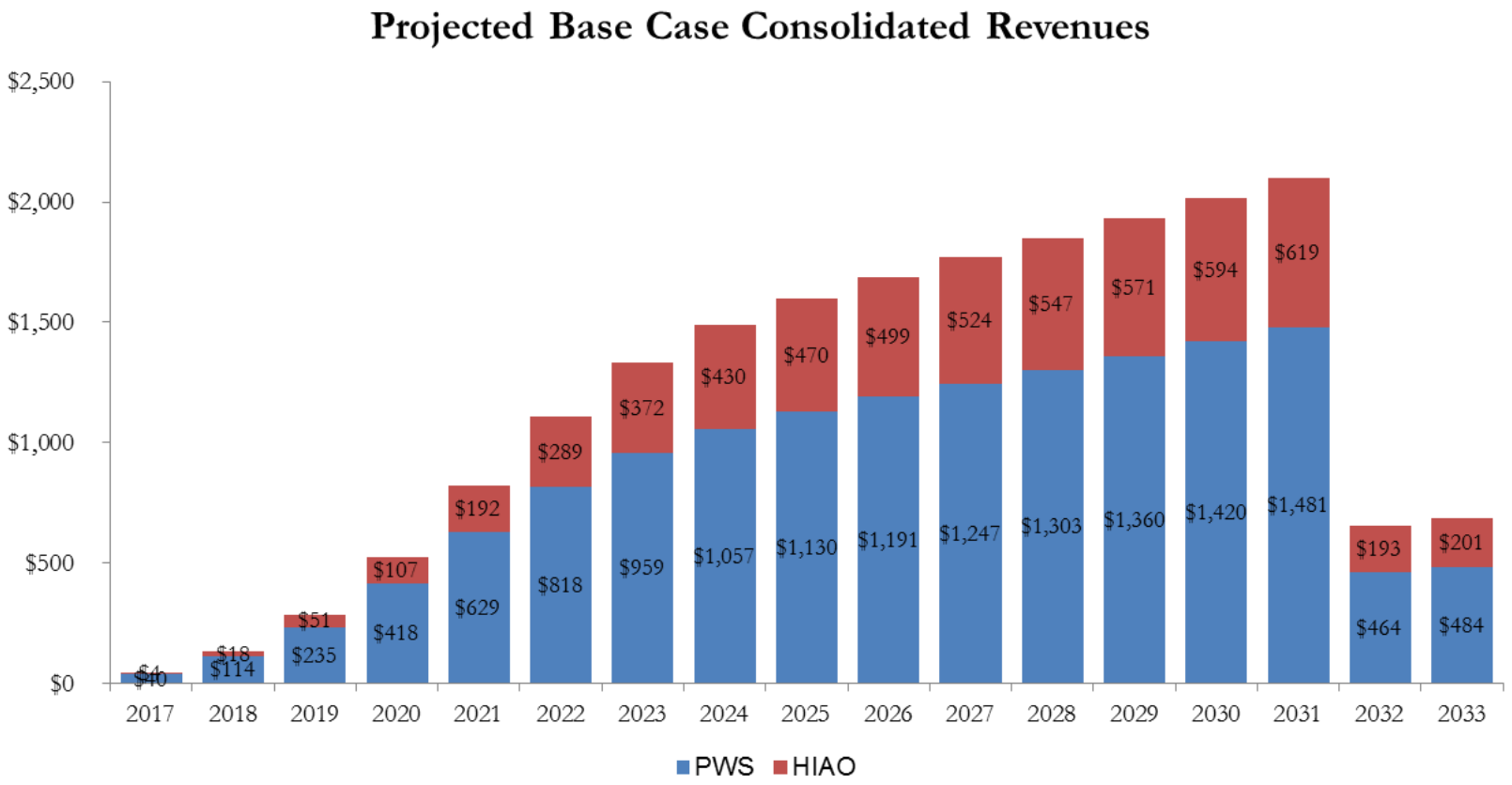
We project risk-adjusted base case revenues of >$1.5bn by 2025, with ~75% revenues from PWS



V. Valuation

DCF valuation ranges suggest a compelling margin of safety – asymmetric upside risk

Base Case DCF Key Assumptions

Terminal Growth Rate – 0%
Discount Rate – 10.0%
Terminal Year – 2033

Value Per Share

Downside	Base	Upside
$21.76	$41.34	$79.56
15%	65%	20%

Expected Value

$46.05

* Includes Cash ($7.91 per share)

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VI. Recent Events

Change in primary endpoint in PWS & OREX's CVOT trial have led to unwarranted negative sentiment, impacting ZFGN's price ~20-30% and providing an excellent entry point to purchase

- **Orexigen CVOT Interim Analysis for Contrave did not show any improvement in cardiac outcomes**
  - Should not affect ZFGN since targeting body weight and hyperphagia in orphan indication, but stock down >10% since announcement…

- **Q1 2015 Earnings Call**
  - Strong relationships developed with key US and EU PWS advocacy organizations.
  - Upsizing of PWS Phase III US & EU Trials due to exceptional interest
  - ZAF-311 endpoint changed to co-primary endpoint of total body weight & hyperphagia-related behavior
    - Concern unwarranted due to impressive 20 point differential seen for 1.8mg beloranib in Phase II, vs. 4.5 point delta needed for Ph. 3 endpoint
  - Potential for NDA in PWS based solely on US Phase III trial results, in Q216

Sources: UCLA, Columbia University College of Physicians & Surgeons

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VI. Conclusion - Risks & Mitigation

Zafgen's biggest risks are associated with regulatory approval of its pipeline drugs, but current results present little cause for concern.

Risk	Mitigant
Zafgen's success entirely hinges on the approval and commercialization of beloranib	Numerous trials have already been conducted proving safety and efficacy. • Completed Phase 2 PWS; currently Phase 3 • Completed Phase 2b HIAO • Completed Phase 2a severe obesity
Competitors may develop/have similar products and reduce Zafgen's potential market share	• Study results show that beloranib leads to a higher reduction in body weight, best in class efficacy • Among all its competitors, Zafgen has the lead in terms of earliest expected go-to-market date, in orphan indications
Zafgen has just begun costly Phase 3 trials for PWS and they currently have no revenue	• Investors retain confidence in Zafgen's products and are willing to continue supplying funds • Once to market, beloranib has blockbuster potential and can generate revenue to fund development of other pipeline drugs

Sources: Zafgen 10-K Report

VI. Conclusion

ZFGN is a Long Term BUY

- Undervalued Growth Potential in the Obesity Market
  - Likely to achieve first-to-market status for beloranib in orphan obesity diseases (PWS and HIAO)
  - Superior efficacy in the orphan disease market will serve as proof of concept for early-stage general obesity treatments in pipeline--opportunity to enter the high growth obesity market
- Misunderstood Change in PWS Phase III Primary Endpoints
- Experienced Management Team & Strong Institutional Backing
- Attractive M&A Target
  - Unpartnered company with late-stage drug candidates in high growth markets
    - Ex-US, ex-EU commercialization opportunity for PWS & HIAO
  - Opportunity for cost synergies (high op-ex)

Current Price*: $32.60

Target Price: $46.05

Upside: 41%

Program	2015	2016
Beloranib *PWS*	• Complete enrollment in US Phase 3 trial • Initiate EU Phase 3 trial mid 2015	• 6 month results from US 'bestPWS' trial by early Q1 • Initiate pediatric program • Injector device development
Beloranib *HIAO*	• Establish US/EU regulatory path • Obtain orphan designation in US and EU	• Initiate Phase 3 program
Beloranib *Severe Obesity*	• 6 month Phase 2b data readout Q4 2015 / very early Q1 2016	• Complete Phase 2b • Development decision point
ZGN-839 *NASH*	• Complete preclinical profiling • File IND mid 2015	• Complete Phase 1 PK/ Safety/Tolerability trials
Second-Generation MetAP2i *Obesity*	• Complete preclinical profiling • Development candidate nomination	• IND Q1 • Initiate Phase 1 trial

*As of 6/3/2015

Appendix

Appendix

Competitor Analysis

Treatment	% Placebo-Adjusted Weight Loss*	Key Limitations**
Phentermine	Variable	• Short-term (a few weeks) use only • Should not be taken during pregnancy
Xenical®/alli	3%	• Unpleasant gastrointestinal side effects related to dietary fat malabsorption • Should not be taken during pregnancy
Qsymia®	6.6% at target dose of 7.5mg/46 mg 8.6-9.4% at high dose of 15mg/92mg	• Known human teratogen – cannot be used in women unless contraception can be assured
Belviq®	3.1-3.3%	• Should not be taken during pregnancy or by women who are planning to become pregnant
Contrave	2.0-4.1%	• Patients should be monitored for suicidal thoughts and behaviors (black box warning, antidepressant class labeling) • Should not be taken during pregnancy
Saxenda®	3.7-4.5%	• Should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (black box warning) • Should not be taken during pregnancy

Sources: Zafgen 10-K Report