Zafgen™

Investor Overview

August 2018

Forward-Looking Statement

These slides and the accompanying oral presentation contain forward-looking statements and information. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward looking statements. For example, all statements we make regarding the initiation, timing, progress and results of our nonclinical and clinical studies and our research and development programs, our ability to advance product candidates into, and successfully complete, clinical studies, and the timing or likelihood of regulatory filings and approvals, and our expected cash, cash equivalents and marketable securities at year end and Zafgen’s expectations regarding the length of its cash runway are forward looking. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These statements are also subject to a number of material risks and uncertainties that are described in our most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Investment Highlights

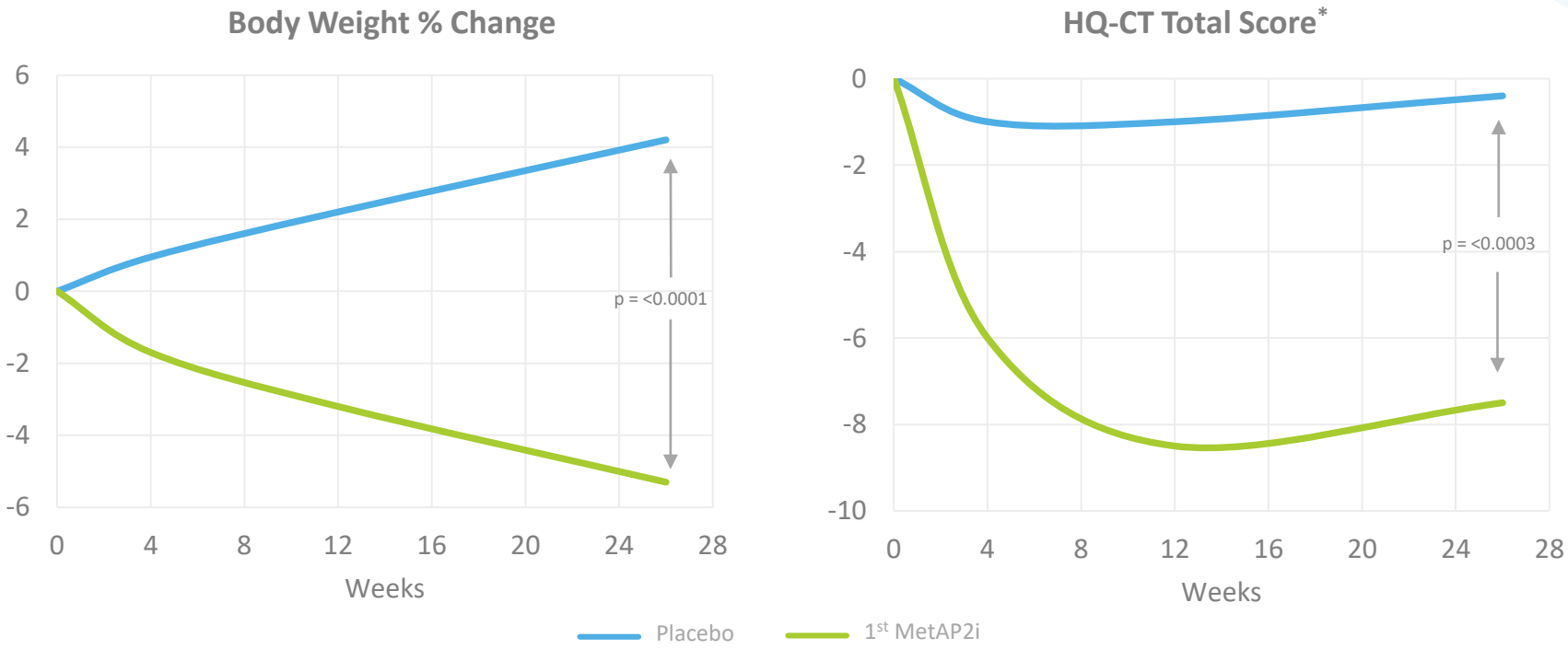
- **A rare disease focused clinical stage biopharmaceutical company with a pipeline of novel therapies that address unmet need in a variety of metabolic diseases**
- **Proprietary, novel MetAP2 biology platform**
  - Validated target; prototype inhibitor demonstrated best-in-field efficacy in multiple metabolic diseases
  - 2nd generation chemistry provides improved safety profile, differentiation among assets, extended patent life into 2036
- **ZGN-1258 for rare metabolic diseases; returning to Prader-Willi syndrome (PWS) first**
  - IND-enabling studies underway; Phase 1 expected to begin in 4Q 2018
  - Multiple nonclinical studies accepted for presentation at Annual Foundation for Prader-Willi Research (FPWR) Conference
  - 4 year natural history study 'PATH for PWS' initiated with FPWR
- **ZGN-1061 for complex type 2 diabetes**
  - Phase 2 proof-of-concept trial presented at ADA; trial achieved all primary objectives
  - Favorable safety and tolerability profile in trial a potential read-through for second generation pipeline
  - NASH potential with ZGN-1061 highlighted by positive nonclinical data also presented at ADA
- **June 30, 2018 cash position of $76M**
  - Pro forma balance of $140M, including proceeds of common stock offering completed in July

Prader-Willi Syndrome

- Approximately 200,000 patients worldwide (~1:40,000)
  - Most common genetic cause of life-threatening obesity
- Characterized by unrelenting pathologic hunger (hyperphagia), and a very low basal metabolic rate
- Hyperphagia dominates thought processes
  - Individuals struggle with concentration, social interaction; impacts ability to attend school, work
  - Overwhelming cravings set up potential lifelong conflict with family members, caregivers
  - Food seeking behaviors can become dangerous
- Low metabolic rate (~800 calories / day) drives increasing, severe obesity
- Average life expectancy ~32 years
- Doctor has no clear therapeutic option

Prader-Willi Syndrome Experience

- First MetAP2i candidate validated on both co-primary endpoints, with clinically important and highly statistically significant impact in prior Phase 3 clinical experience

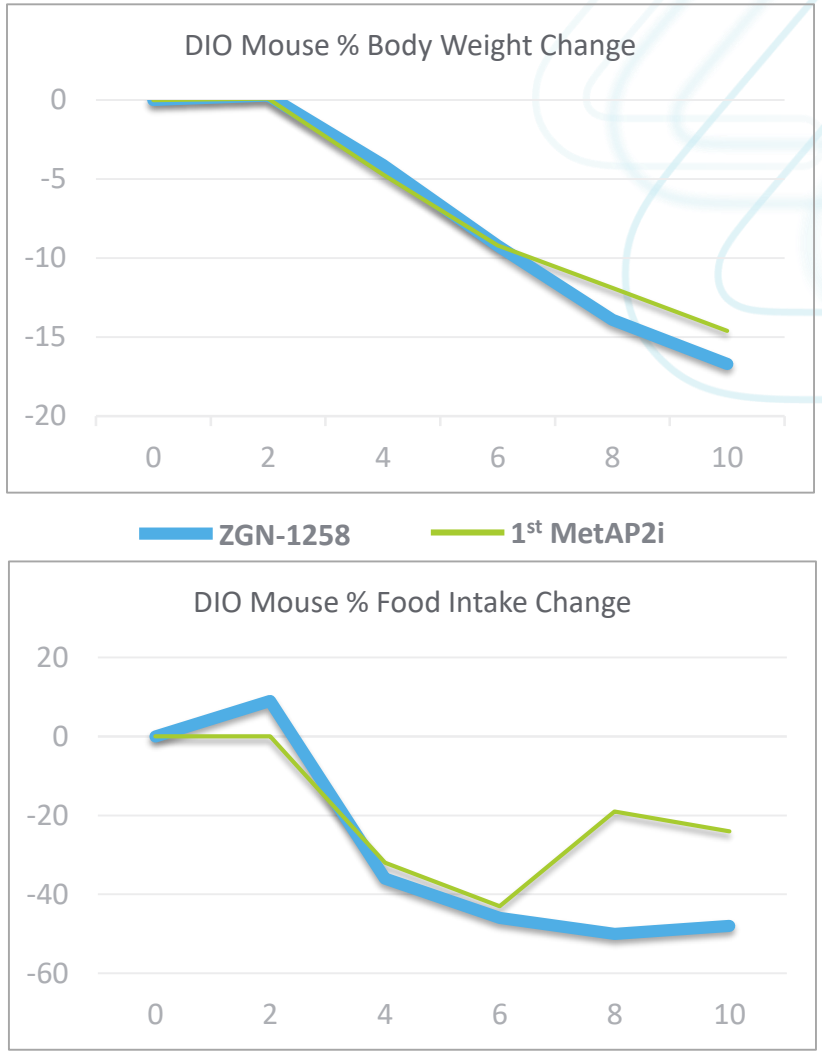


- Well tolerated AE profile; observed as generally equal to placebo
- Endothelial cell issue arose halting progression of first MetAP2i

*HQ-CT Score assesses hyperphagia-related behaviors; developed by Zafgen, donated to FPWR, broadly adopted by FDA and industry

ZGN-1258 Nonclinical Profile

Endpoint	ZGN-1061	ZGN-1258	1st MetAP2i
Tissue Distribution	Preferential to adipose tissue and liver	Preferential to CNS, adipose tissue and liver	Broadly distributed
MetAP2 Enzyme IC_{50}, nM	3.7	6.5	4.0
Mouse DIO Efficacy (10 Day - 0.3mpk - % weight loss)	16.7%	17.7%	15.7%
Rat DIO Efficacy (10 Day - 0.3mpk - % weight loss)	5.7%	6.8%	6.5%
Mouse ob/ob Efficacy Model of Hyperphagia and Obesity	Higher doses required for efficacy	Robust weight loss, reduced food intake	Robust weight loss, reduced food intake
Dog Pharmacokinetics	Rapid Clearance (<8h)	Rapid Clearance (<8hr)	Slow Clearance (>24hrs)
Dog Thrombosis	>100x margin	>100x margin	<5x margin



ZGN-1258 Advancing Towards Clinic

- **ZGN-1258 advanced into IND-enabling studies 1Q 2018**
  - ZGN-1258 extensively vetted nonclinically; size, scope and duration of completed nonclinical studies exceeds what is typically seen for Phase 1 initiation
- **Multiple nonclinical studies accepted for presentation at Annual FPWR Conference** (October 4-7th)
  - Effects on food intake and body weight
  - Effects in various models of behavioral manifestations commonly observed in PWS
  - Differentiation vs first-generation compound
  - PATH for PWS natural history study design
- **IND allowance and initiation of Phase 1 anticipated in 4Q 2018**
- **Company expects to leverage prior experience in PWS to enhance / accelerate ZGN-1258 development**

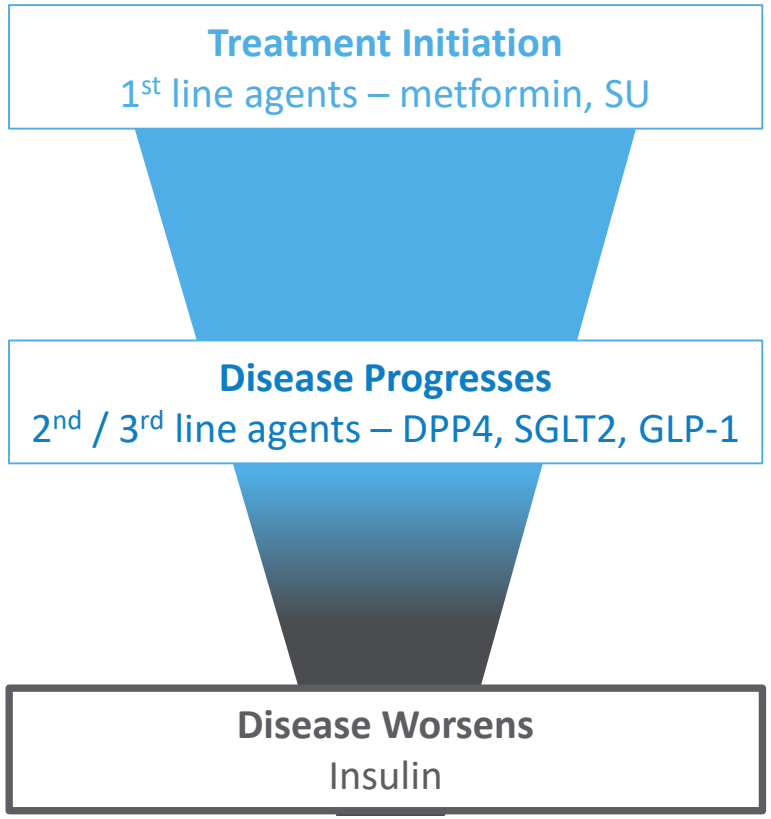
PATH for PWS – Natural History Study

- **Non-interventional study in PWS, conducted in partnership with FPWR**
  - Caregivers will provide update every 6 months
  - Advances the collective community's knowledge of the medical history and medical events in people with PWS
- **Potential benefits of natural history study for Zafgen**
  - Provides context for benefits of treatment and any adverse events
  - Participants in PATH for PWS study eligible for ZGN-1258 clinical trials; may facilitate enrollment
  - Participants may be referenceable as extended alternate control group for ZGN-1258 clinical trials, increasing study efficiency

PATH for PWS™
Paving the way for Advances in Treatments & Health for PWS

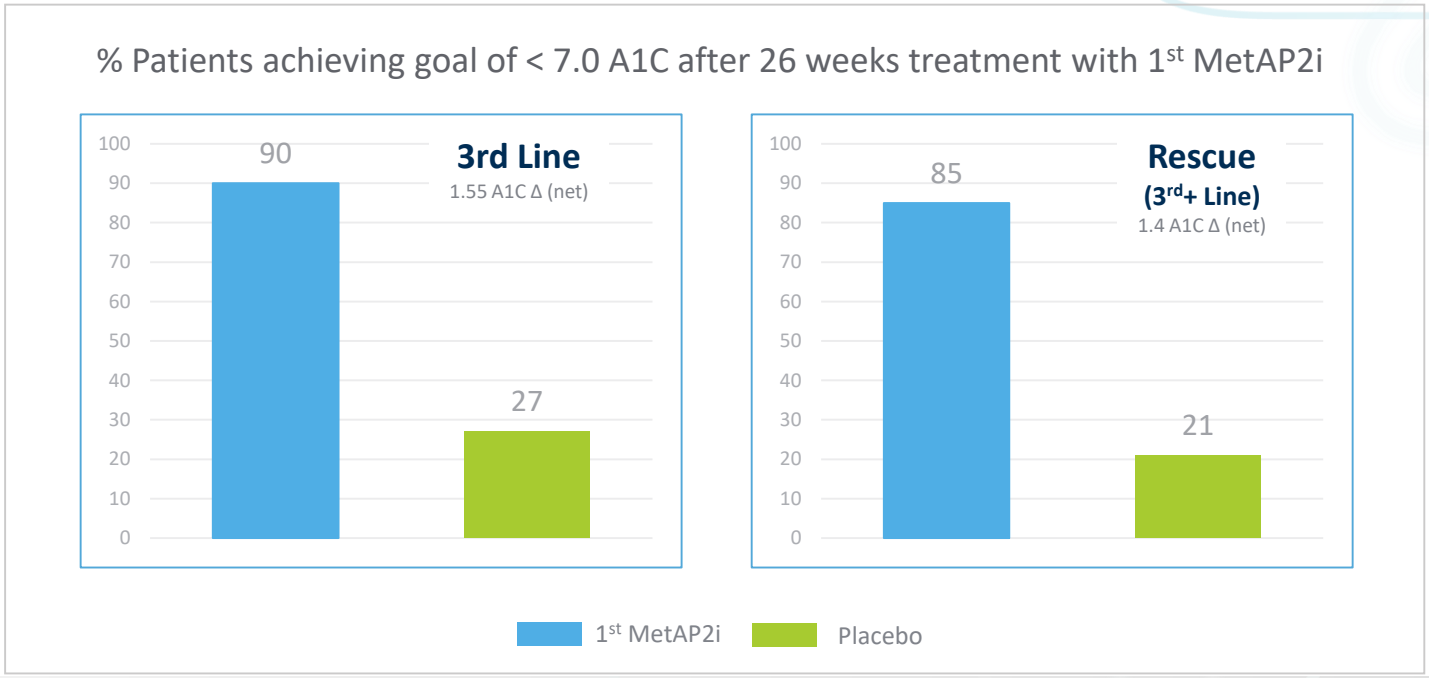
FOUNDATION FOR PRADER-WILLI RESEARCH
Working Toward an Independent Future

ZGN-1061 Market Opportunity



- **$20B annual insulin sales in T2DM**

- Typical patient progressing to insulin is complex:
  - Insulin resistant, A1C > 8.0, pan-metabolic dysregulation (LDL, weight, NASH)
- Opportunity for novel therapeutic that offers complementary and significant A1C effects in later lines of therapy



Positive Results from Phase 2 Proof-of-Concept Trial

- Phase 2 data for ZGN-1061, a novel MetAP2 inhibitor in development for difficult to control type 2 diabetes, recently presented at ADA
- Positive data reinforce excitement for potential of ZGN-1061
  - Met all primary endpoints delivering a statistically significant reduction in A1C at 12 weeks with 0.9 mg compared to placebo, with a trend indicating the potential for further A1C reduction beyond 12 weeks
  - Highly tolerable safety profile, unusually high study completion rate of 95% and no evidence of CV safety issues
  - Low-to-mid level target engagement doses studied; 0.9 mg identified as minimally effective dose
  - Patient dosing recently initiated in new 1.8 mg cohort to explore higher end of the potential therapeutic range
- Nonclinical data also presented at ADA provide support for additional unique value

Phase 2 Proof-of-Concept Clinical Trial

Objective:

- Evaluate efficacy and safety of ZGN-1061 at a low-to-mid dose in patients with difficult to control type 2 diabetes who are failing other anti-diabetic agents

Expectations for trial:

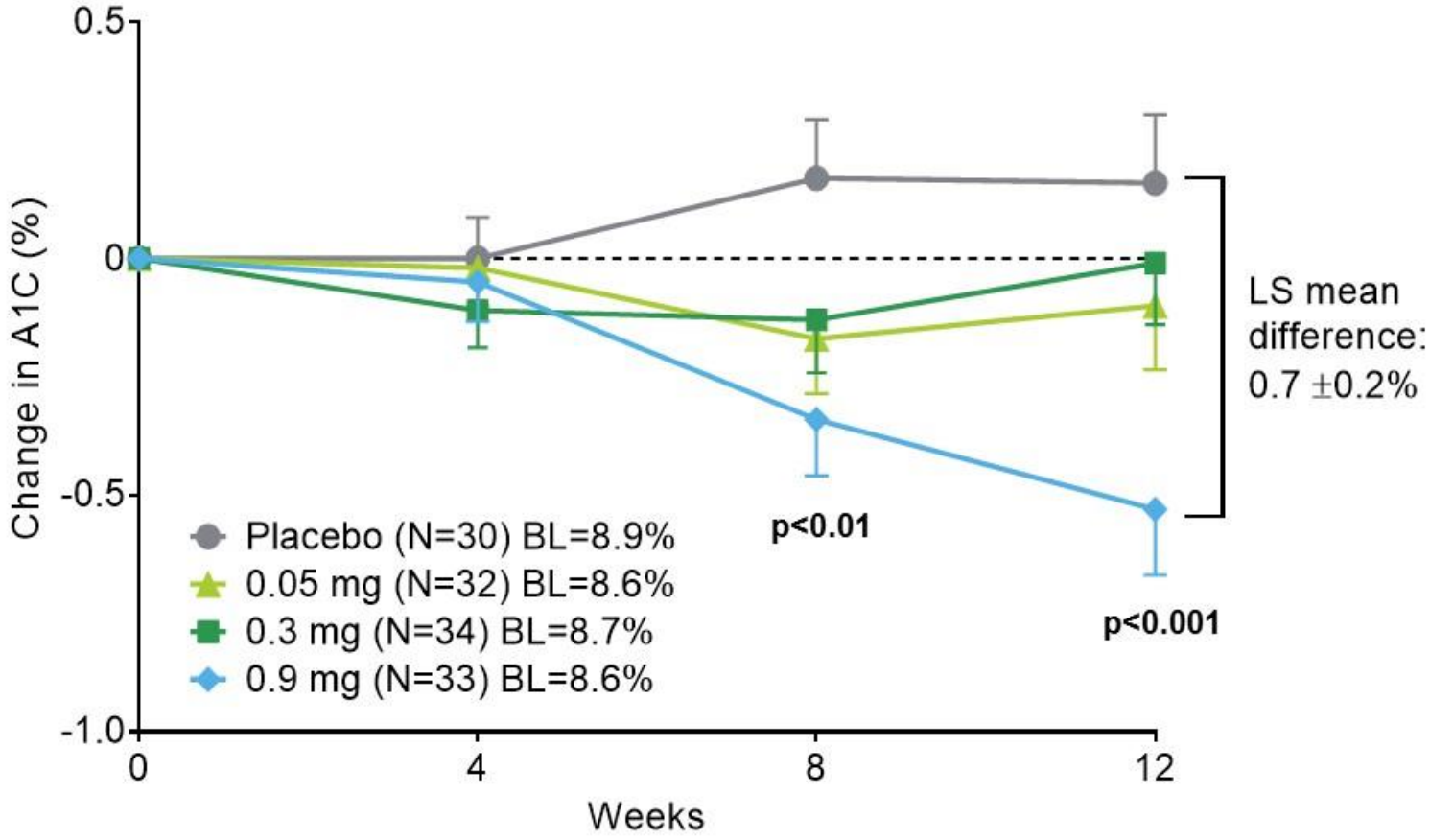
- Demonstrate favorable safety and tolerability profile
- Demonstrate dose response -- particularly to explore / understand low end of dose curve (up to ~50% target engagement) and establish a minimally effective dose

	0.05 mg (n=32)	0.3 mg (n=34)	0.9 mg (n=33)	Placebo (n=30)
A1C, %	8.64 ± 1.0	8.73 ± 1.1	8.69 ± 1.1	8.87 ± 1.2
BMI, kg/m^2	36.0 ± 6.5	37.9 ± 7.2	36.8 ± 8.1	37.0 ± 5.5
Number of Glucose-Lowering Medications				
None	3 (9.4)	1 (2.9)	0	4 (13.3)
1	12 (37.5)	16 (47.1)	14 (42.4)	10 (33.3)
2	11 (34.4)	12 (35.3)	14 (42.4)	13 (43.3)
≥3	6 (18.8)	5 (14.7)	5 (15.2)	3 (10.0)

Data are mean ±SD or number and percent of patients for the ITT/safety populations (N=129).
A1C=hemoglobin A1C, BMI=body mass index

ZGN-1061 Produced a Progressive and Statistically Significant Improvement in A1C for 0.9 mg ZGN-1061

- Statistically significant reduction in A1C for 0.9 mg vs placebo at Weeks 8 and 12
- A1C continued to decline with no waning of effect for 0.9 mg dose through Week 12



Data are LS mean ±SE for the ITT population (N=129). MMRM analysis
BL=baseline

ZGN-1061 Generally Safe and Well Tolerated

- Adverse events primarily mild or moderate with overall study completion rate of 95%
- Most frequent AEs were injection site bruising, upper respiratory tract infection, and diarrhea
- Two patients (both 0.9 mg ZGN-1061) reported SAEs (upper abdominal pain, skin ulcer); neither deemed related to study drug
- No CV safety signals observed in trial

Most Frequent Adverse Events (Incidence ≥ 5% in Total ZGN-1061 Group)

	0.05 mg N=32	0.3 mg N=34	0.9 mg N=33	Total ZGN-1061 N=99	Placebo N=30
Any AE	20 **(62.5)** 59	28 **(82.4)** 91	27 **(81.8)** 76	75 **(75.8)** 226	24 **(80.0)** 62
Injection Site Bruising	4 **(12.5)** 4	5 **(14.7)** 6	3 **(9.1)** 3	12 **(12.1)** 13	5 **(16.7)** 5
Upper Respiratory Tract Infection	3 **(9.4)** 3	5 **(14.7)** 5	2 **(6.1)** 2	10 **(10.1)** 10	2 **(6.7)** 2
Diarrhea	**0**	5 **(14.7)** 5	4 **(12.1)** 4	9 **(9.1)** 9	2 **(6.7)** 2
Headache	1 **(3.1)** 1	2 **(5.9)** 2	3 **(9.1)** 3	6 **(6.1)** 6	2 **(6.7)** 4
Pain In Extremity	**0**	4 **(11.8)** 4	2 **(6.1)** 2	6 **(6.1)** 6	1 **(3.3)** 1
Arthralgia	1 **(3.1)** 1	3 **(8.8)** 3	2 **(6.1)** 2	6 **(6.1)** 6	**0**
Back Pain	2 **(6.3)** 2	2 **(5.9)** 2	1 **(3.0)** 1	5 **(5.1)** 5	**0**

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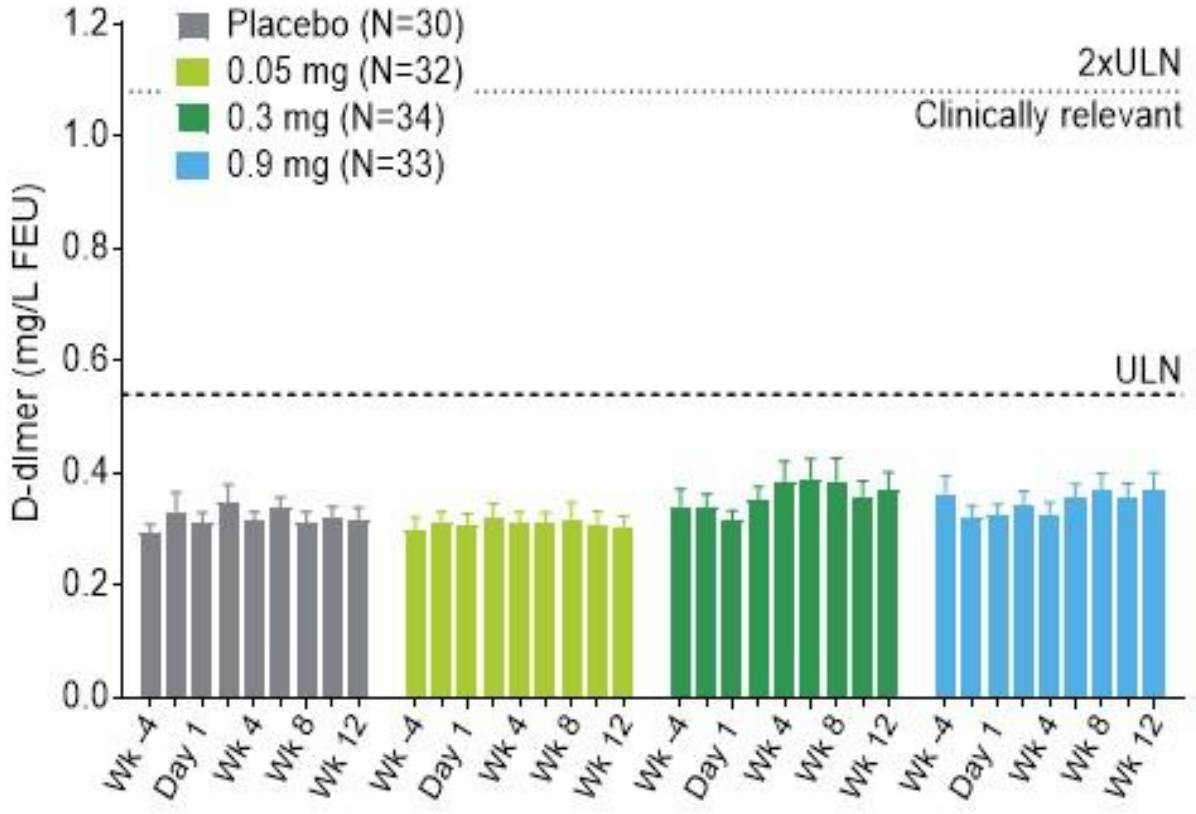
Data are number and percent of patients and number of events for the safety population (N=129) during randomized treatment.
*AE=adverse event, SAE=serious adverse event

ZGN-1061 No D-Dimer or Other CV Safety Signals

- No meaningful elevations in mean D-dimer concentrations across the dosing groups compared to baseline or placebo
- No notable changes in markers of coagulation/ hypercoagulability and no cases of potential VTE for adjudication by the Data Monitoring Committee



Baseline D-dimer levels for all patients every 2 weeks through 12 week period

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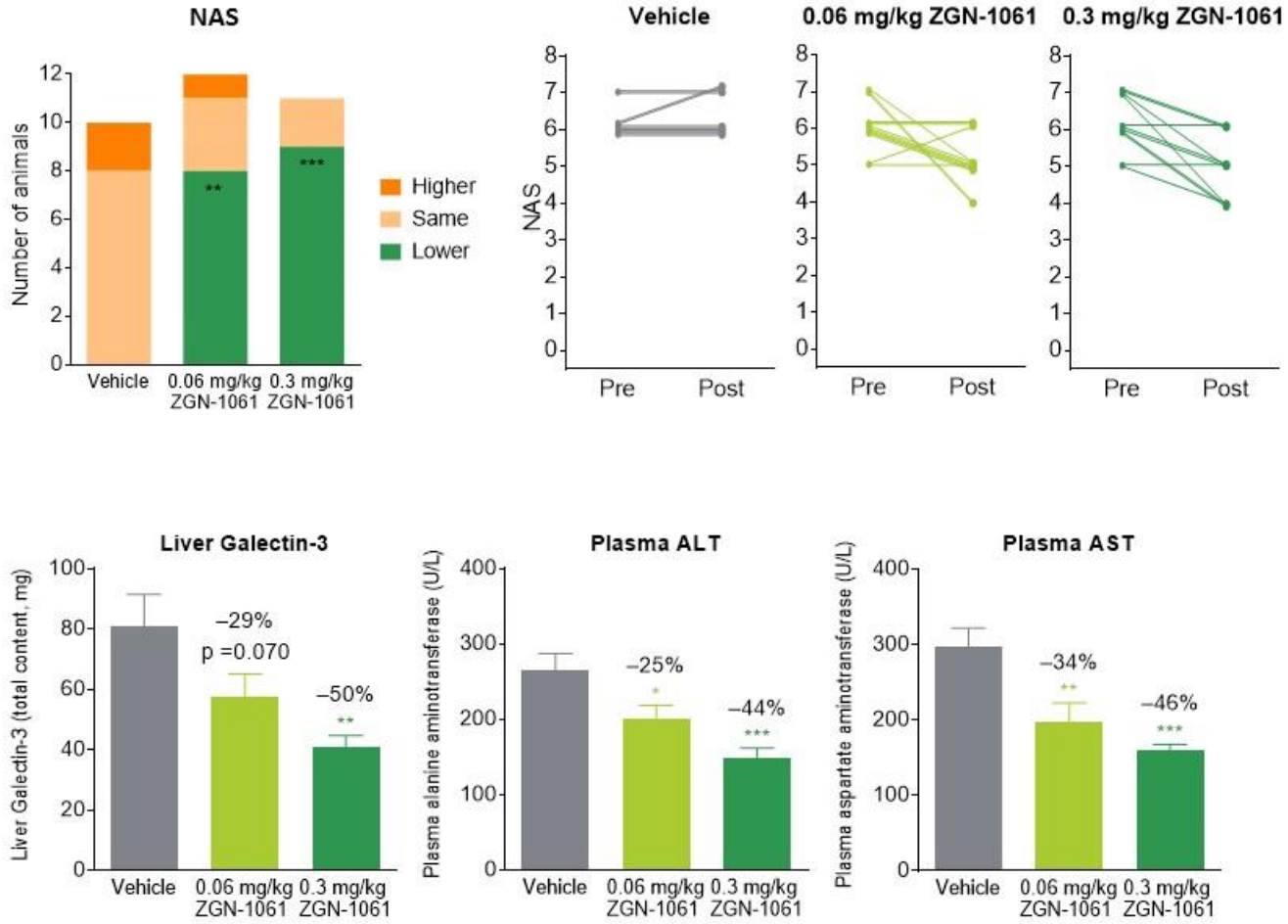
Data are mean ±SE for the safety population (N=129). Age-adjusted upper limit of normal (ULN=0.54 mg/L FEU) indicated by dashed line. 2xULN=1.08 mg/L FEU
FEU=fibrinogen equivalent unit, ULN=upper limit of normal, VTE=venous thromboembolism
D-dimer is a fibrin degradation product that becomes markedly elevated during a VTE

ZGN-1061 Demonstrates Improvement in DIO-NASH Model

- Reduced NAS from baseline
- Improved markers of liver damage
- Reduced liver weight and liver content (triglycerides and cholesterol)



Summary of histopathological scoring of the pre- and post-study biopsies. For each group the number of animals with a higher (worsening), same, or lower (improvement) score at post- compared to pre-study is indicated by the height of the bar. For each compound group, significance of number of animals with a lower score was assessed using Fisher's exact test followed by adjustment for multiple correction using the Bonferroni method. **p<0.01, ***p<0.001 compared to Vehicle. Abbreviations: NAFLD = nonalcoholic fatty liver disease, NAS = NAFLD activity score

Data are mean and SEM (n=10-12/group). Data were analyzed by one-way ANOVA with Dunnett's Multiple Comparison Test. *p<0.05, **p<0.01, ***p<0.001 compared to Vehicle. Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, SEM = standard error of the mean

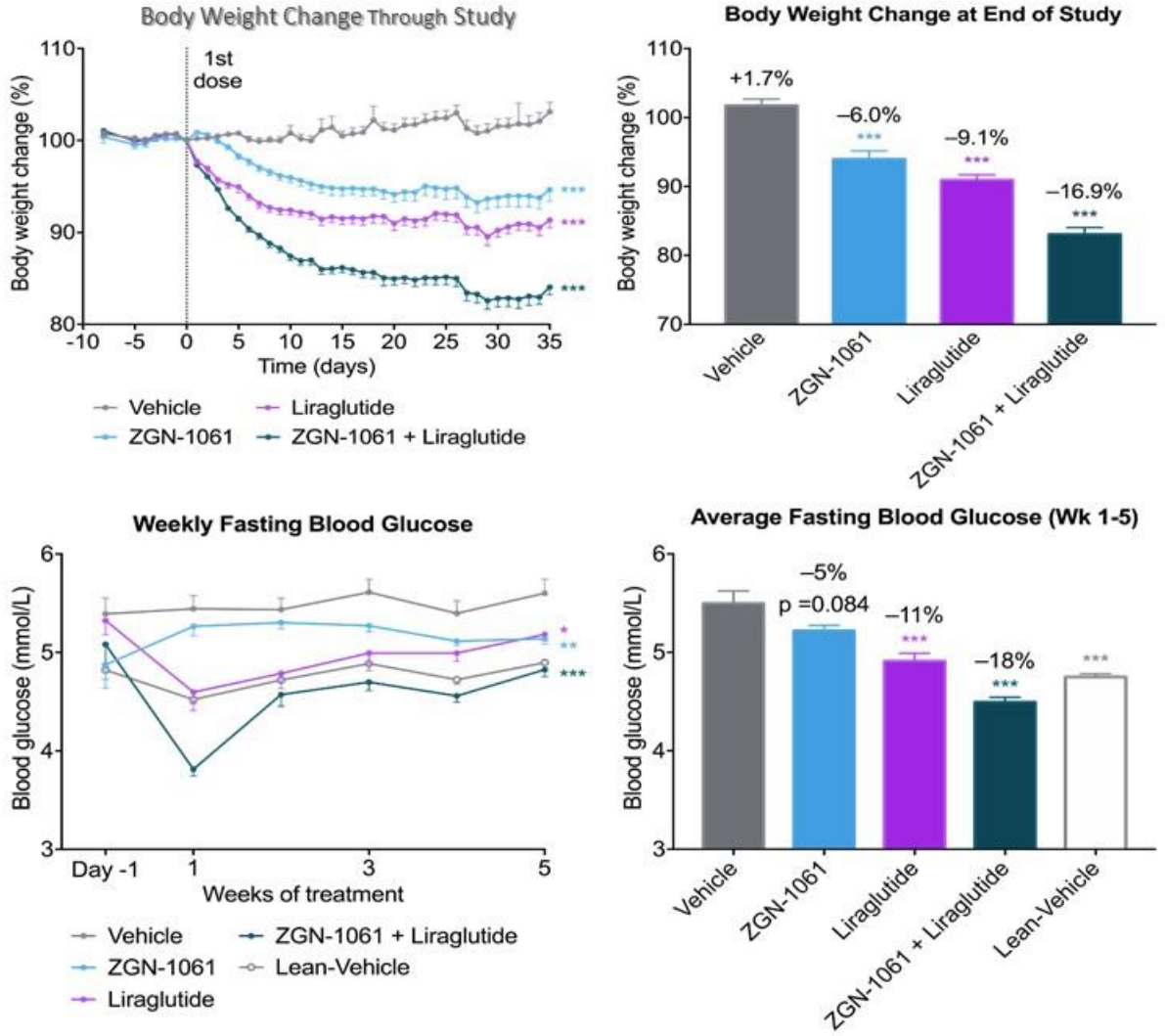
ZGN-1061 in Combination with Liraglutide Reduces Body Weight and Improves Glycemic Control in Diet Induced Obesity (DIO) Rat Model

Study Design

- Randomized 5 week once-daily SC treatment with either 0.3 mg/kg ZGN-1061, 0.4 mg/kg liraglutide, a combination treatment of ZGN-1061 + liraglutide, or vehicle (5% mannitol)
  - Liraglutide equivalent to maximum dose; ZGN-1061 generally equivalent to 0.9 mg dose
- Tested for changes in body weight and glycemic control in 4 study groups

Results

- Weight loss within first 5 days of treatment and sustained through duration of 35-day study
  - Weight loss was additive, implying complementary MOA
- Combination treatment significantly lowered weekly FBG



Percent change in body weight relative to Day 0. Data are mean and SEM (n=10/group). Mean absolute body weights on Day 0 were 657 ±17 g for vehicle, 659 ±15 g for ZGN-1061, 655 ±15 g for liraglutide, 656 ±14 g for ZGN-1061 + liraglutide, and 495 ±7 g for lean-vehicle. Data were analyzed by two-way ANOVA and Tukey's post-hoc test. Only significant differences on the last day of treatment are indicated (left figure). ***p<0.001 compared to Vehicle. Abbreviations: SEM = standard error of the mean

Fasting (4h) blood glucose. Data are mean and SEM (n=10/group). Data were analyzed by two-way ANOVA (Weekly FBG endpoint) or one-way ANOVA (Average FBG for Wk 1-5) and Tukey's post-hoc test. Only significant differences on the last day of treatment are indicated (left figure). Percentages are relative to Vehicle (right figure). *p<0.05, **p<0.01, ***p<0.001 compared to Vehicle. Abbreviations: SEM = standard error of the mean

ZGN-1061 Next Steps in 2018

- Complete remaining ongoing six / nine month toxicology studies
- Progress 1.8 mg cohort to understand efficacy of full target engagement
- IND allowance by FDA anticipated in 4Q 2018, to enable future clinical work in the US
- Further explore positive liver effects of ZGN-1061 to understand potential for benefit in NASH
- Review comprehensive data sets with KOLs and potential partners

2018 Pipeline Milestones

Program	Milestones	Timing
ZGN-1061 for type 2 diabetes	• ADA abstract presentations • Phase 2 core proof-of-concept data • IND allowance for future clinical trials *	June 2018 ✓ Mid-2018 ✓ 4Q 2018
ZGN-1258 for rare metabolic disease (Prader-Willi syndrome)	• IND-enabling studies initiation • Natural history study initiation • IND / Phase 1 initiation	1Q 2018 ✓ Mid-2018 ✓ 4Q 2018
Pipeline liver program	• Development candidate and indication selection	4Q 2018

- $76M cash position as of June 30, 2018; pro forma cash balance of $140M including proceeds of common stock offering completed in July 2018
- Expect balance of greater than $100 million at year-end

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* Current Ph 2 trial being conducted in Australia and New Zealand, allowed company to accelerate time to data and decrease trial cost ~43.5% due to Australia R&D incentives

Pathway Platform

Purpose

Advancing insight-driven MetAP2 therapeutics to transform the lives of patients with complex metabolic disorders

Zafgen™