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American Diabetes Association 78th Scientific Sessions Investor & Analyst Update Call

June 25, 2018

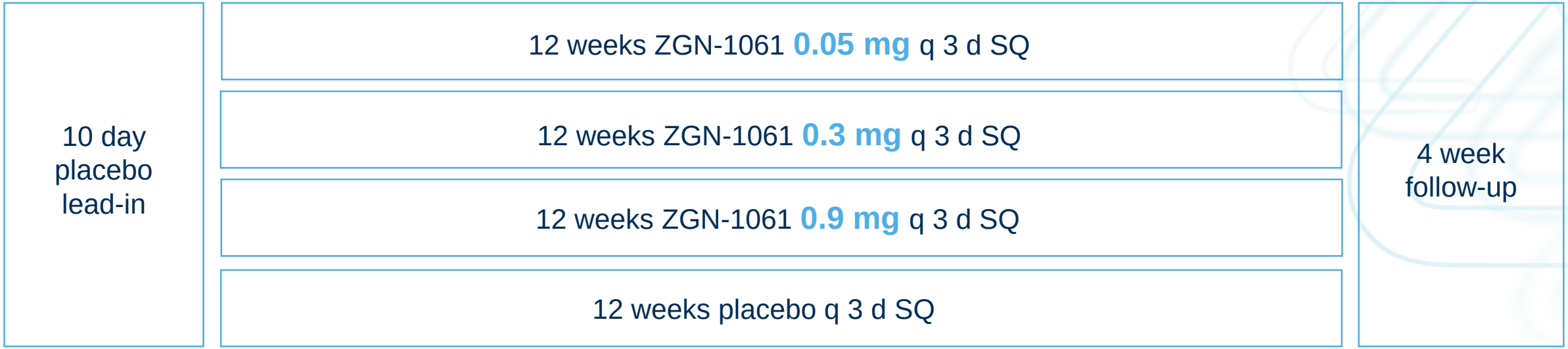
Forward-Looking Statement

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 pre-clinical 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.

Highlights for ZGN-1061 from ADA

- Phase 2 data for ZGN-1061, a novel MetAP2 inhibitor in development for difficult to control type 2 diabetes, 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 continuing trend for A1C reduction
  - 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 as minimally effective dose
  - Patient dosing recently initiated in 1.8 mg cohort to explore higher end of the potential therapeutic range
- Nonclinical data also presented at ADA provide additional support
- Data support ongoing partnering activities

Phase 2 Proof-of-Concept Clinical Trial Design



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 already failing multiple 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 and establish minimally effective dose
    - Qualitative efficacy signals seen in Phase 1b across full 0.2 mg – 1.8 mg dosing spectrum

Baseline Demographics Well-Balanced Across Dosing Groups

	0.05 mg N=32	0.3 mg N=34	0.9 mg N=33	Placebo N=30
Age, y	55.8 ± 7.6	53.9 ± 9.3	54.9 ± 7.6	52.8 ± 8.2
% Male	56	38	61	57
% White/Asian/Other	78/3/19	68/6/26	82/0/18	83/0/17
Duration of T2D, y	8.0 ± 6.0	7.2 ± 5.8	8.4 ± 5.6	7.6 ± 5.2
A1C, %	8.64 ± 1.0	8.73 ± 1.1	8.69 ± 1.1	8.87 ± 1.2
FPG, mg/dL	195.6 ± 50.9	195.6 ± 60.8	194.7 ± 49.6	205.3 ± 45.8
Body Weight, kg	105.6 ± 23.2	107.3 ± 22.3	105.8 ± 25.8	107.5 ± 16.2
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)
Any	29 (90.6)	33 (97.1)	33 (100.0)	26 (86.7)
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)

Nearly all randomized patients completed (95%, 122/129) Week 12

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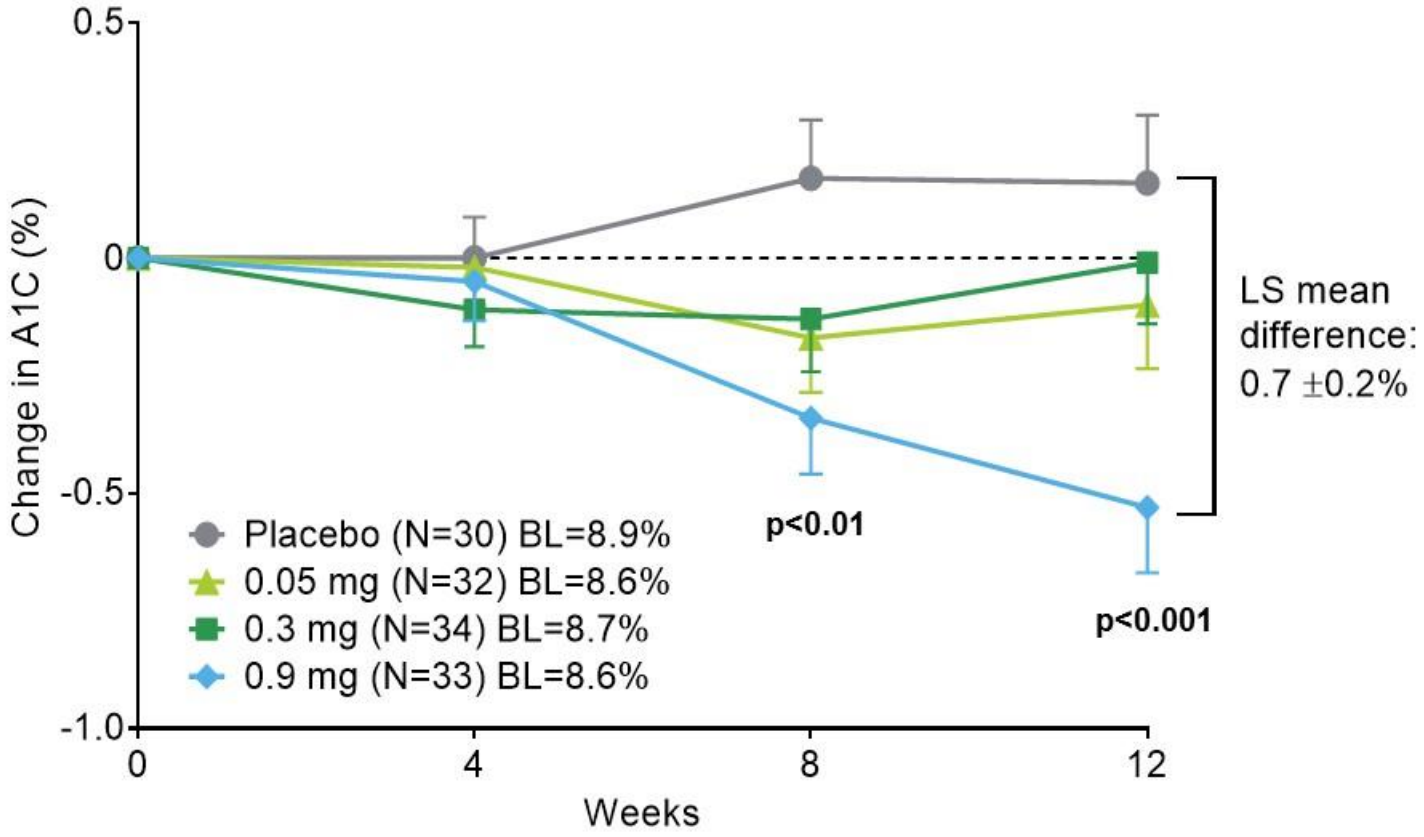
Data are mean ±SD or number and percent of patients for the ITT/safety populations (N=129).
A1C=hemoglobin A1C, BMI=body mass index, FPG=fasting plasma glucose, T2D=type 2 diabetes

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

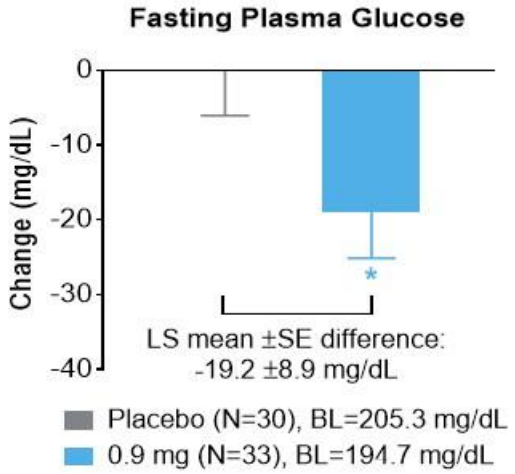
- Statistically significant reduction in A1C for 0.9 mg vs placebo at Weeks 8 and 12
- A1C continued to decline with no waning of effect through Week 12 for 0.9 mg dose
- No meaningful change in A1C with lower doses (0.05 mg and 0.3 mg)
- Study amended to evaluate a higher dose (1.8 mg) compared with additional 0.9 mg and placebo groups
  - 1.8 mg is expected to approximate full target engagement

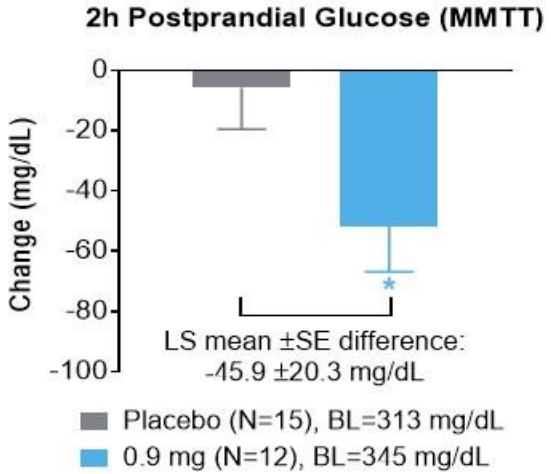


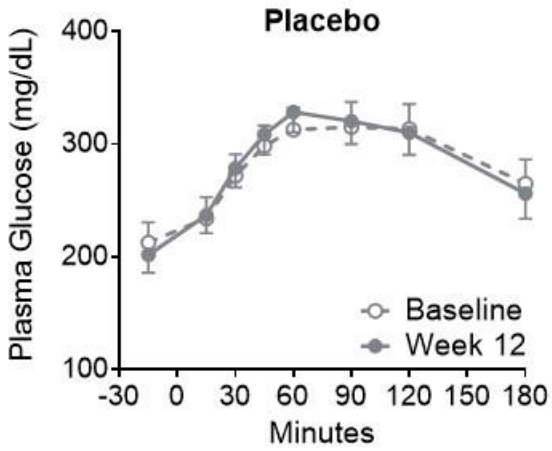
Data are LS mean ±SE for the ITT population (N=129). MMRM analysis
BL=baseline

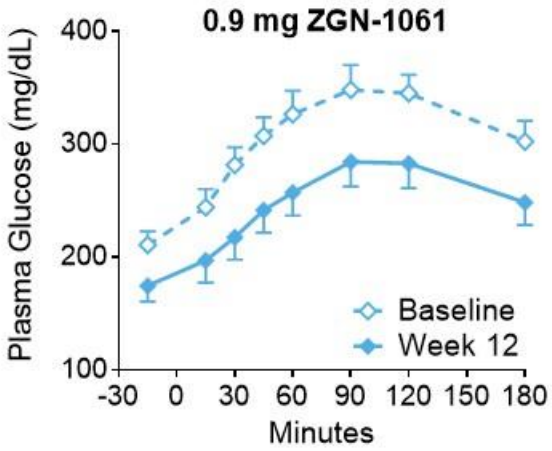
ZGN-1061 Improved Measures of Glycemic Control

- Statistically significant reduction in fasting plasma glucose (FPG) for 0.9 mg dose vs placebo at Week 12
- In a subset of participants who underwent Mixed Meal Tolerance Test (MMTT)
  - ZGN-1061 reduced 2h Postprandial Glucose (PPG)









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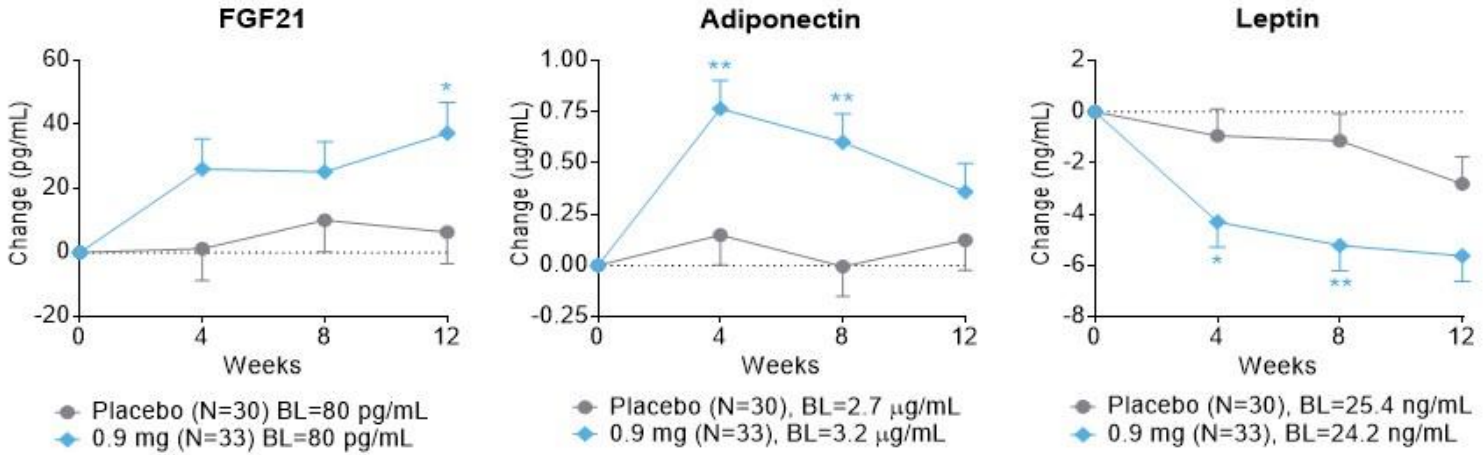
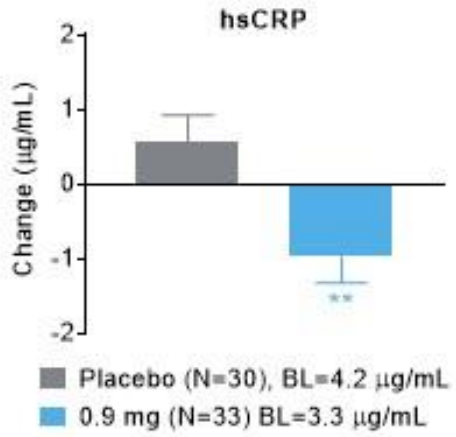
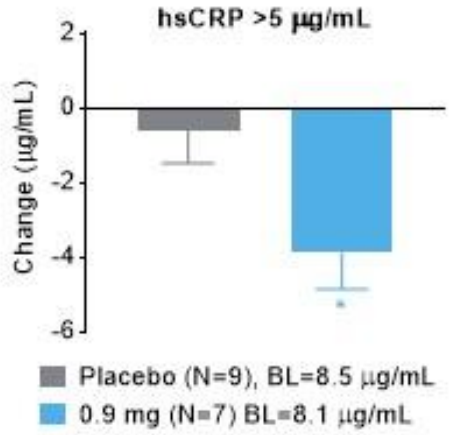
FPG data are LS mean ±SE change from baseline to Week 12 for the ITT population (N=129), MMRM analysis. PPG data are LS mean ±SE change from baseline to Week 12, ANCOVA analysis, for the MMTT population (N=63). Standardized meal provided at 0 min after overnight fast; study drug administered 1h prior to meal. *p<0.05.
Data are LS mean ±SE (table) or mean ±SE (figure) for the MMTT population (N=63). Insulinogenic index = Δinsulin(0–30)/Δglucose(0–30)

ZGN-1061 Improved Additional Secondary Measures

- Improvements in FGF21, adiponectin, and leptin for ZGN-1061 0.9 mg dose vs placebo
- Additional trends in lipid improvements for ZGN-1061 vs placebo
- Moderate weight loss observed for both ZGN-1061 (-1.5 ±0.4 kg, BL 105.8) and placebo (-0.9 ±0.4 kg, BL 107.5) at Week 12
- Strong improvement in hsCRP







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Data are LS mean ±SE change from baseline to Week 12 for the ITT population (N=129), MMRM analysis. *p<0.05, **p<0.01
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BL=baseline, FGF21=fibroblast growth factor 21, hsCRP=high sensitivity C-reactive protein

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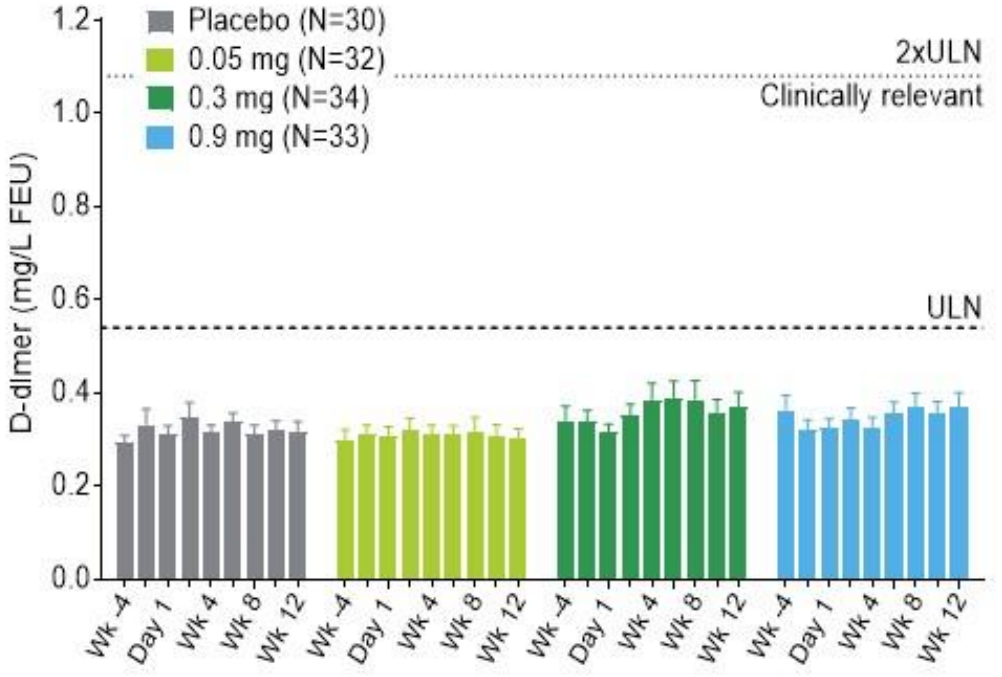
Data are number and percent of patients for the safety population (N=129) during randomized treatment.
*AE=adverse event, ECG=electrocardiogram, SAE=serious adverse event

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
  - D-dimer level increases are indicative of pro-thrombotic effect with prior MetAP2 inhibitor, which demonstrated frequent significant increases
- No notable changes in markers of coagulation/ hypercoagulability and no cases of potential VTE for adjudication by the Data Monitoring Committee
- No meaningful changes observed in other safety laboratory measures: blood pressure, heart rate or ECG's
- Rapid absorption and clearance of ZGN-1061 from circulation observed



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

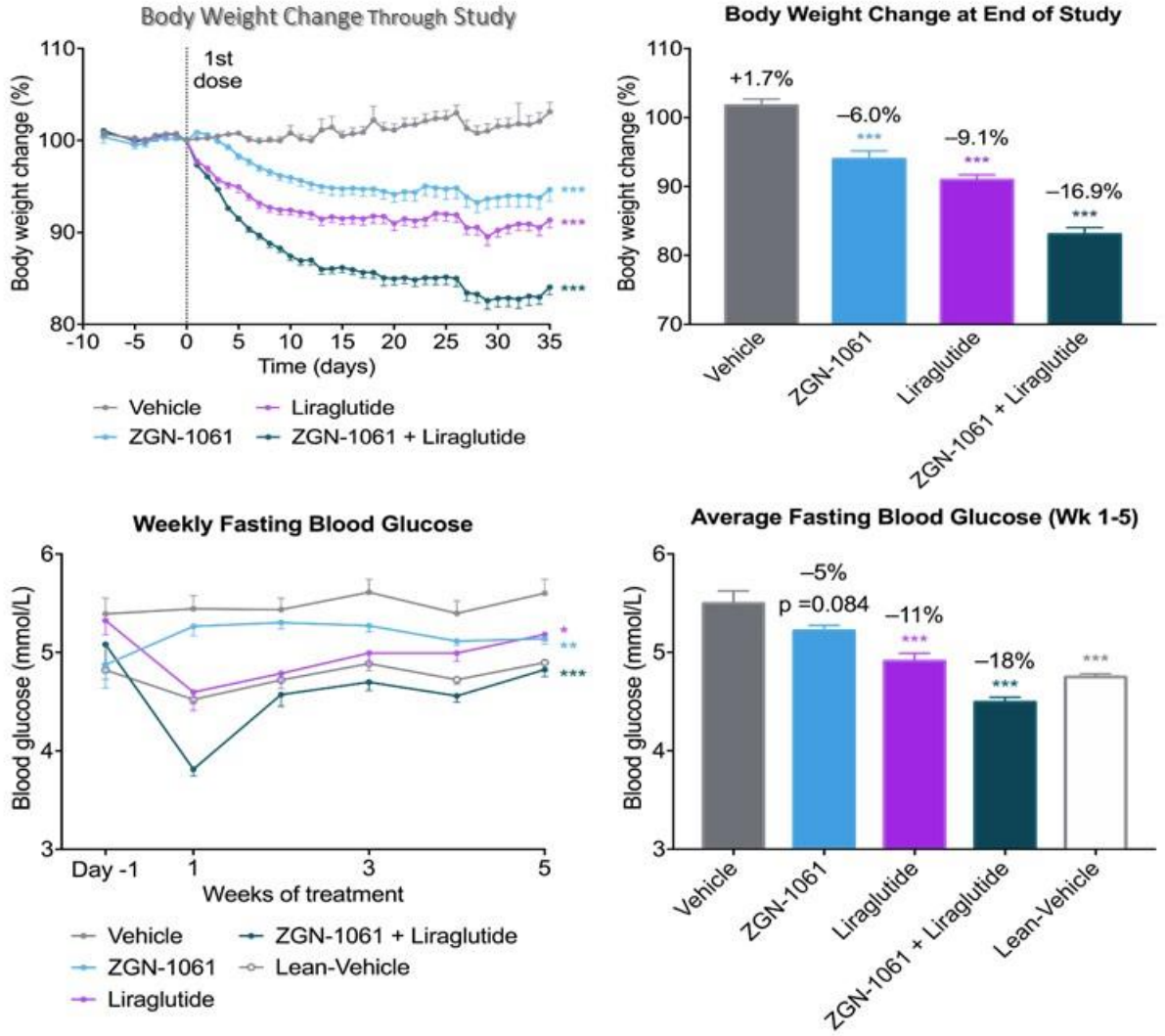
ZGN-1061 in Combination with Liraglutide Reduces Body Weight and Improves Glycemic Control in Diet Induced Obesity (DIO) Rat Model

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

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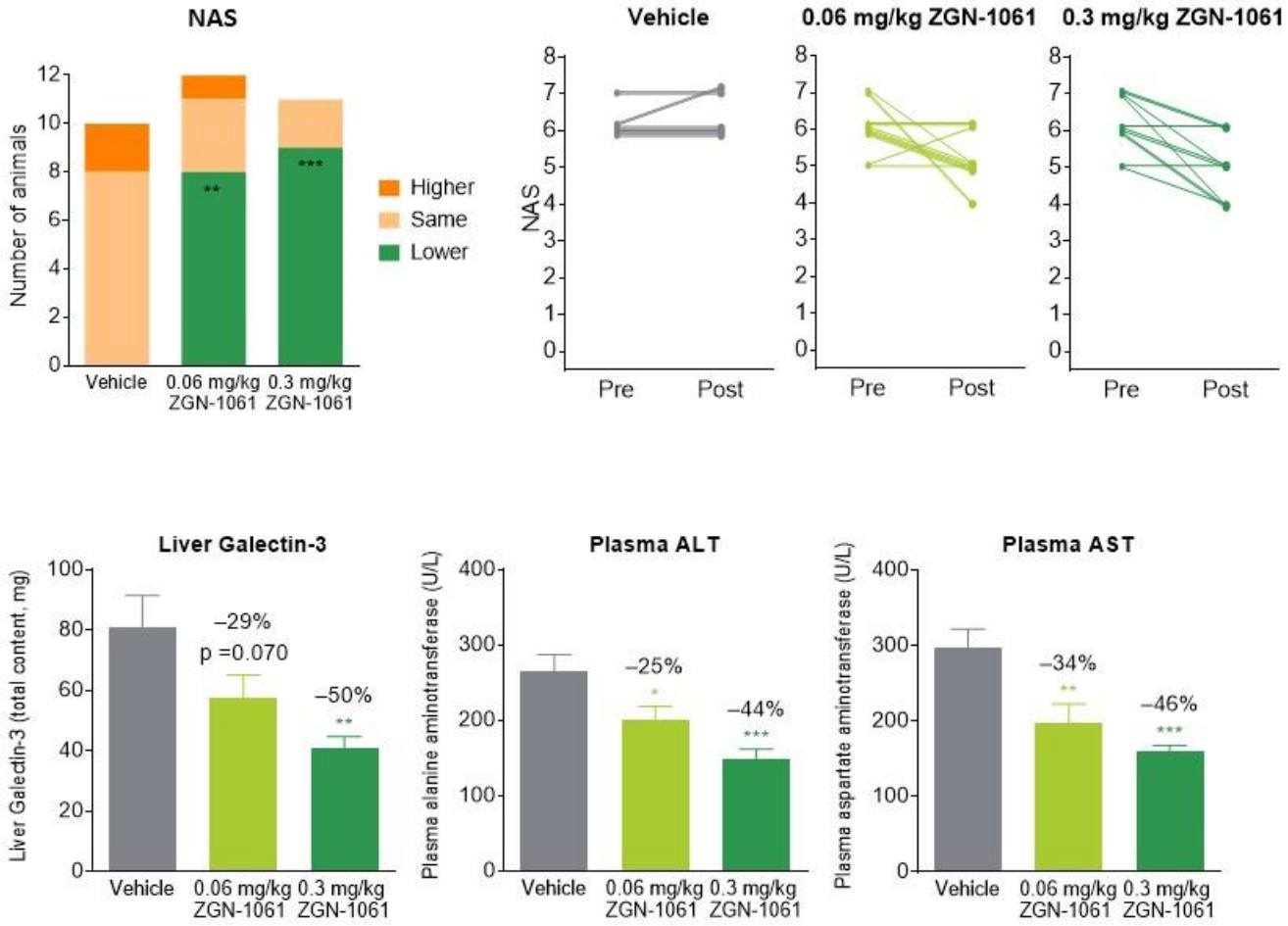
ZGN-1061 Demonstrates Improved Metabolic Parameters in Biopsy-Confirmed DIO-NASH Mouse Model

Study Design

- DIO nonalcoholic steatohepatitis (DIO-NASH) mice were randomized to receive once daily SC treatment with 0.06 mg/kg ZGN-1061, 0.3 mg/kg ZGN-1061, or vehicle (5% mannitol) for 37 weeks prior to and throughout study
- Tested liver weight, NAFLD Activity Score (NAS), hepatic pathology, and other metabolic parameters
- Measurements taken after 8 weeks

Results

- Reduced NAS from baseline
- Improved markers of liver damage
  - Reduced galectin-3 and plasma ALT and AST
- Reduced liver weight and liver content (triglycerides and cholesterol)
- 0.3 mg dose treatment exhibited greater improvements in metabolic parameters than placebo and low dose



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

Conclusions

Phase 2 Proof-of-Concept Clinical Trial

- ZGN-1061 met all primary endpoints at 0.9 mg dose
- Highly statistically significant A1C lowering with 0.9 mg dose
  - Progressive reduction in A1C with no evidence of a waning effect
  - Consistent and meaningful biomarker improvements in FGF21, adiponectin, leptin, hsCRP and others
- Highly tolerable safety profile comparable to placebo with an unusually high study completion rate of 95% and no CV safety signals

Nonclinical

- ZGN-1061 treatment in combination with liraglutide demonstrates significant weight loss and improves glycemic control and other metabolic parameters with additive effect in DIO rat model
- ZGN-1061 treatment improves NAS and decreases markers of liver damage in DIO-NASH mouse model

ZGN-1061 Next Steps in 2018

- Complete remaining ongoing six / nine month toxicology studies
- Submit IND to FDA
- Progress 1.8 mg cohort
  - To understand efficacy of full target engagement
  - Patient dosing recently initiated
- Further explore positive liver effects in additional nonclinical models
- Review data with KOLs and potential partners
  - Multiple such activities occurred at ADA meeting
  - New CBO, Brian McVeigh, leading partnering discussions – added to executive team May 29th
- Decisions on further steps will follow these activities in 2019

2018 Pipeline Milestones

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

- $89M cash position as of March 31, 2018
- Operating runway into 2H 2019; includes multiple value inflection milestones

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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 ~40% due to Australia R&D incentives