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Investor Overview

June 2019

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, our ability to successfully engage with the FDA concerning the clinical hold on a clinical trial of ZGN-1061, our ability to successfully demonstrate the efficacy and safety of our product candidates and to differentiate our product candidates from first generation MetAP2 inhibitors, such as beloranib, 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 filings with the U.S. 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 product candidates that are intended to address unmet need in a variety of metabolic diseases**

- **ZGN-1061 for type 2 diabetes with concomitant obesity and/or NASH**
  - Diabetes market evolving towards therapies with enhanced A1C lowering efficacy and positive effects on common co-morbidities (obesity/NAFLD)
  - Phase 2 proof-of-concept trial demonstrated significant A1C lowering efficacy and weight loss, with a safety and tolerability profile generally comparable to placebo
  - Nonclinical ZGN-1061 studies have demonstrated significant NASH model efficacy, and complementary efficacy in combination with a GLP-1
  - **Next milestone:** Update on development plans by end of 3Q 2019

- **ZGN-1258 for rare metabolic diseases, including Prader-Willi syndrome**
  - Prader-Willi syndrome is a rare, lethal disease emerging in childhood, with ~200,000 afflicted worldwide; no current therapeutic options available
  - Development plans suspended due to unexpected finding in long-term toxicology studies

- **ZGN-1345 for metabolic liver disease**
  - Multiple metabolic-related liver diseases exist with high unmet medical need, from NAFLD/NASH to hepatocellular carcinoma
  - Compound is an orally dosed MetAP2i with high liver concentrations but minimal-to-no detectable systemic exposure; once daily dosing expected
  - Named as development candidate 4Q 2018; nonclinical development work underway

- **March 31, 2019 cash position of $105M; runway expected to extend through at least 2020**

Type 2 Diabetes Market Opportunities

Large Market with High Unmet Need

415M people worldwide living with type 2 diabetes; expected to grow to 642M by 2040[1]

≥50% of patients have uncontrolled A1C, despite multiple approved treatments available[2]

In the US, every five minutes 14 adults are newly diagnosed and 2 people die of diabetes-related causes[3]

Multiple Co-Morbidities; Evolving Guidelines

High incidence of co-morbidities:

- >75% obese [4]
- >70% cardiovascular diseases [4]
- >22-70% NAFLD/NASH [5]
- >35% renal disease [6]

New 2018 ADA/EASD guidelines are patient-centric, driven by co-morbidities, vs previous algorithms that prioritized generics regardless

Type 2 diabetic market dynamics include increasing focus on: getting A1C to goal (more effective single agents, combination therapy w/ complementary agents) and positive effects 'beyond A1C' that address co-morbidities

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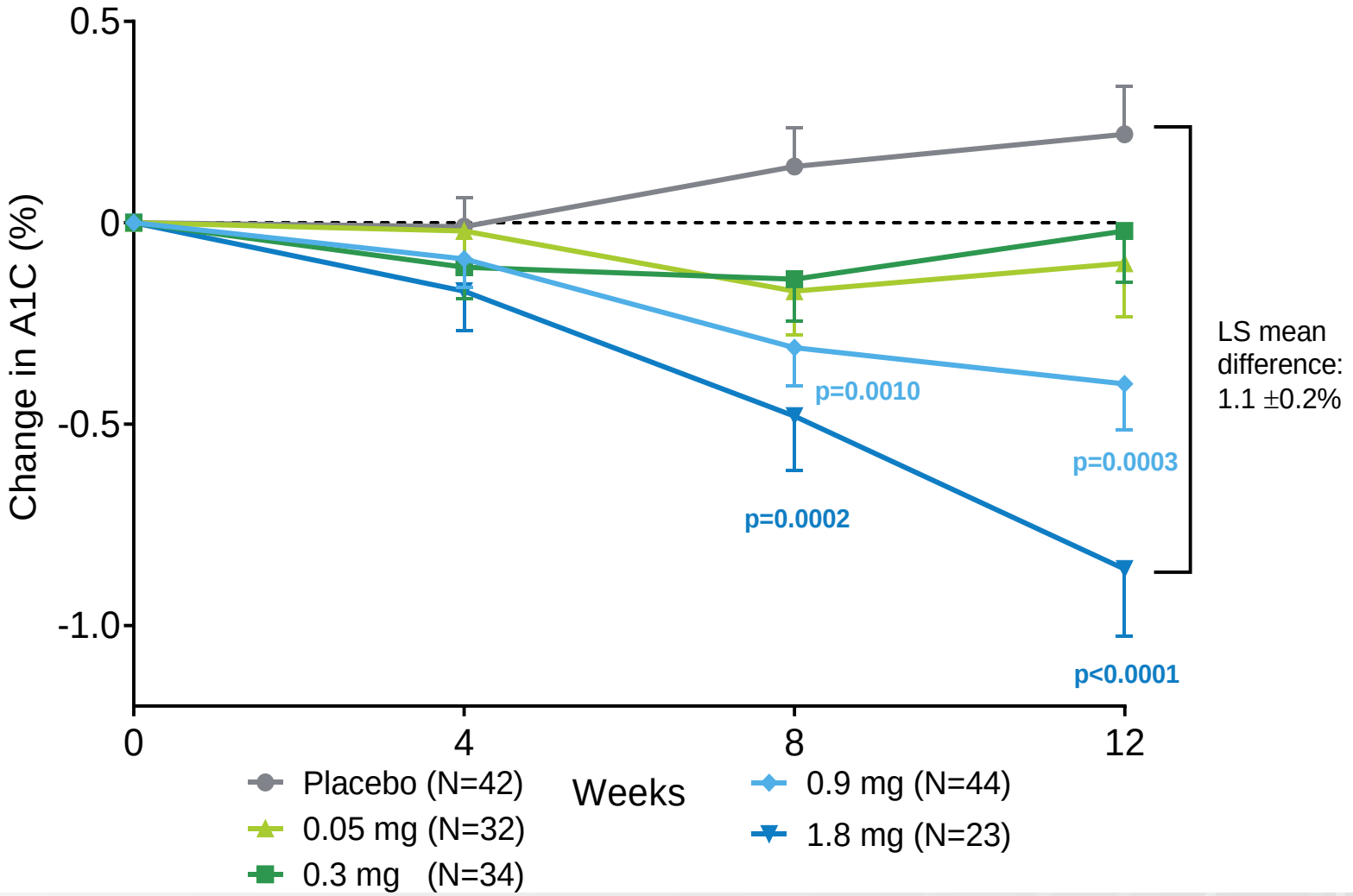
[1] Global Data, Type 2 Diabetes, March 2018; [2] Lipska Diabetes Care Volume 40, April 2017; [3] CDC, November 2018; [4] Curr Med Res Opin. 2016 Jul; [5] Williams et al. 2011 and Bazick et al. 2015; [6] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017

Abbreviations: NAFLD=Nonalcoholic Fatty Liver Disease; NASH=Nonalcoholic steatohepatitis; EASD=European Association for the Study of Diabetes

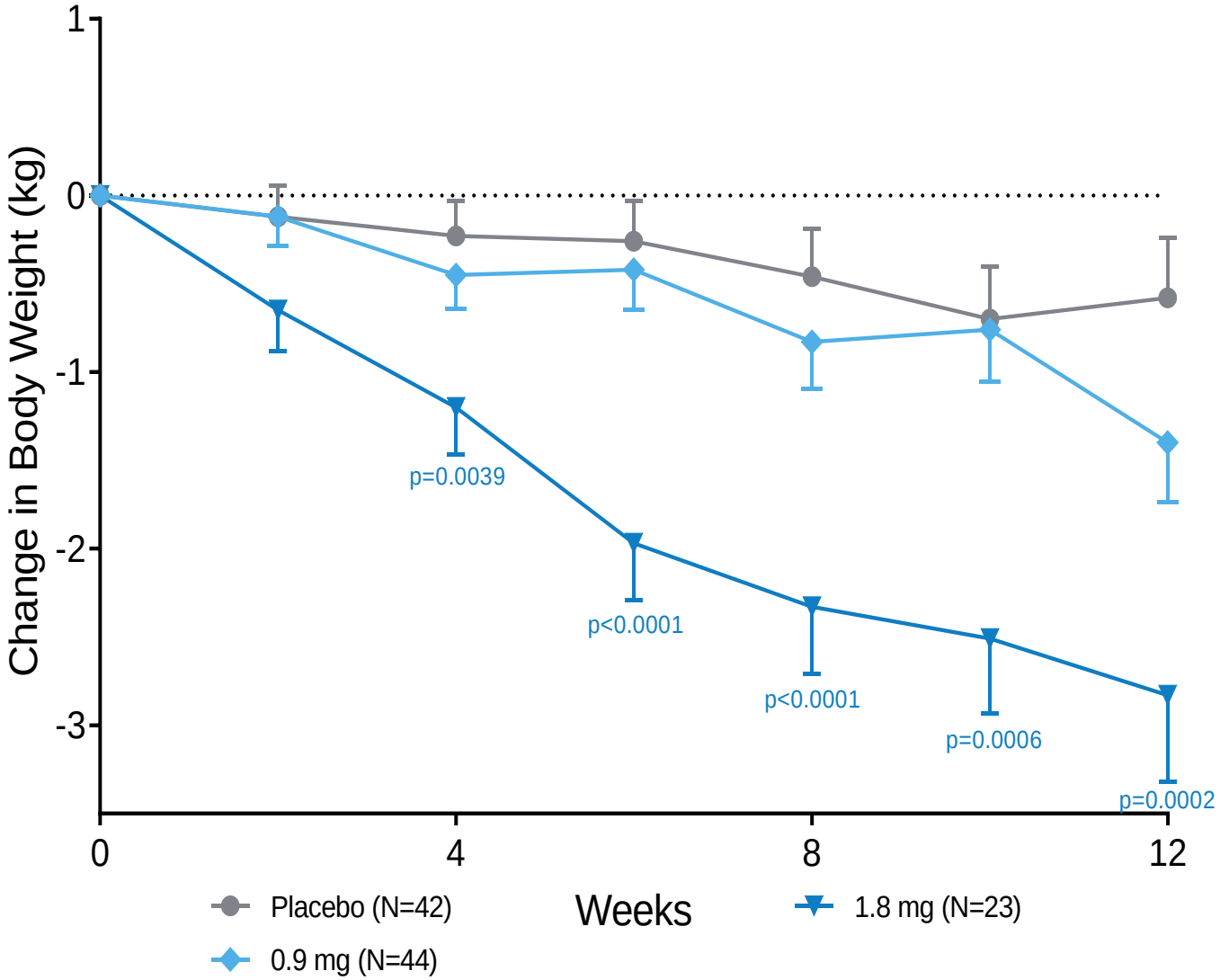
ZGN-1061 A1C Lowering Efficacy in Proof-of-Concept Trial

- Progressive and statistically significant improvement in A1C for 0.9 mg and 1.8 mg vs placebo
- A1C continued to decline with no waning of effect for 0.9 mg and 1.8 mg doses through Week 12
- Fasting plasma glucose changes in trial suggest a further A1C lowering effect with longer duration of treatment



Data are LS mean ±SE for the ITT population (N=175). MMRM analysis

ZGN-1061 Weight Lowering Efficacy in Proof-of-Concept Trial



- Progressive and statistically significant improvement in weight for 1.8 mg vs placebo
- Weight continued to decline with no waning of effect through Week 12
- Weight loss competitive with reported data from best-in-class anti-diabetes therapies at 12 weeks

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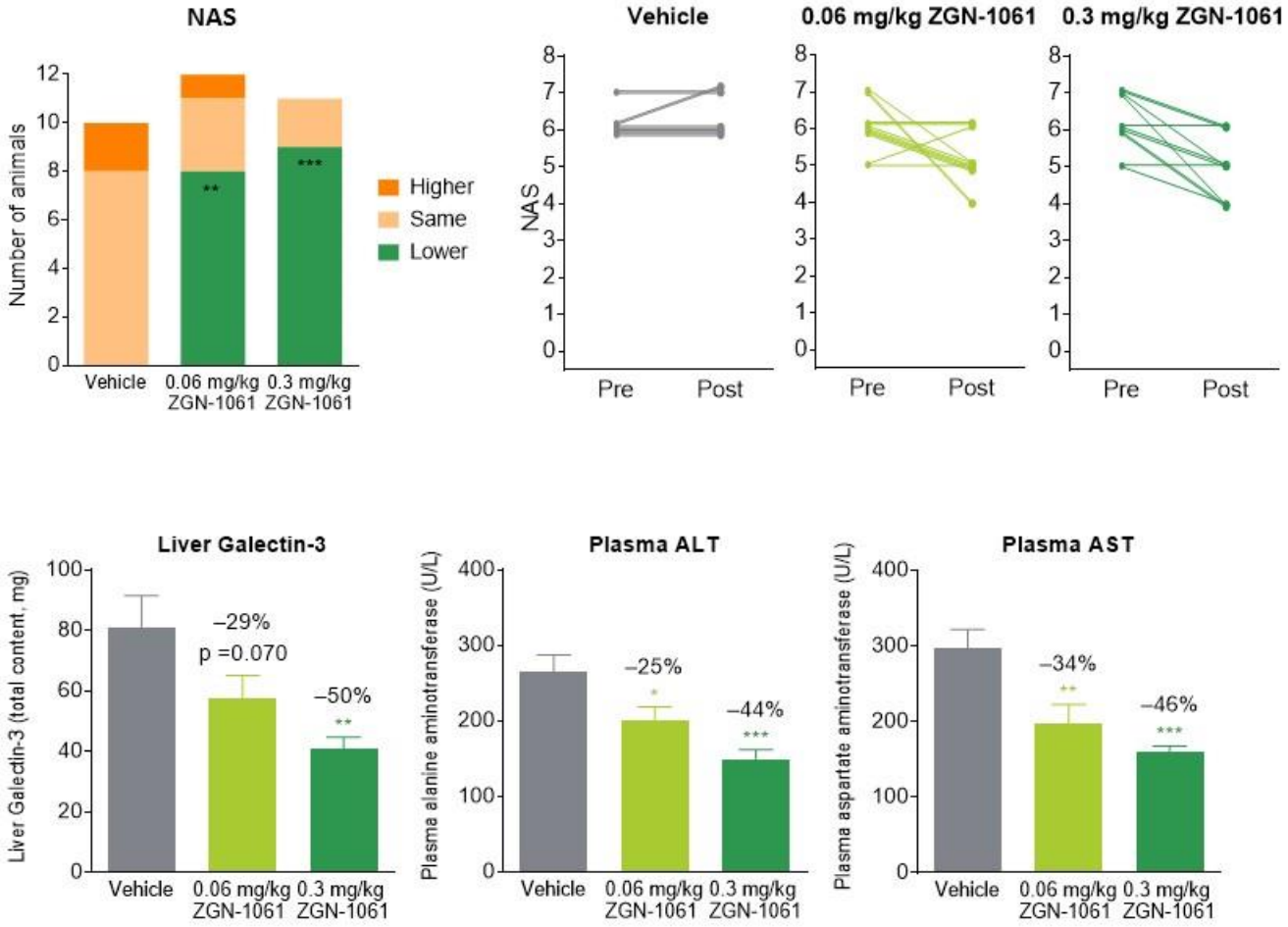
Data are LS mean ±SE for the ITT population (N=175). MMRM analysis

ZGN-1061 Potential Efficacy in NASH Nonclinical Study

- NAS reduced significantly from baseline
- Markers of liver damage improved
- Liver weight and liver content (triglycerides and cholesterol) reduced



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 Early-Stage Safety / Tolerability Summary

Nonclinical

- **Toxicology studies now Phase 3 enabling; ZGN-1061 studied in rats up to 6 months and dogs up to 9 months**
  - Studies support continued advancement in the clinic
  - Not mutagenic or genotoxic at concentrations substantially above expected clinical exposure
  - Overall toxicology supports long-term clinical trials in humans
  - Rapidly absorbed and eliminated by design
  - No significant DDI expected[1]

Phase 1

- **Phase 1a single ascending dose (SAD) trial conducted in 39 normal healthy volunteers**
- **Phase 1b multiple ascending dose (MAD) trial (28 days) conducted in 29 obese healthy volunteers**
- **All doses generally safe and well tolerated in Phase 1 clinical trials**
  - AEs equivalent to placebo
  - No withdrawals due to AE; no SAEs
  - No safety signals

[1] Drug-drug Interaction

ZGN-1061 Safety / Tolerability in Proof-of-Concept Trial (n=175)

- Adverse events primarily mild or moderate; no severe AEs with 1.8 mg
- Three patients (all 0.9 mg) reported SAEs (upper abdominal pain, skin ulcer, anaphylactic reaction to antibiotic); none deemed related to study drug
- Three patients (1.6%) withdrew early due to an adverse event (injection site urticaria, 1.8 mg; upper abdominal pain, 0.9 mg; sensory disturbance, 0.05 mg)
- No CV safety signals observed in trial

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

% of Patients	0.05 mg N=32	0.3 mg N=34	0.9 mg N=44	1.8 mg N=23	Total ZGN-1061 N=133	Placebo N=42
Any AE	62.5	82.4	79.5	91.3	78.2	81.0
Injection Site Bruising	12.5	14.7	11.4	17.4	13.5	21.4
Upper Respiratory Tract Infection	9.4	14.7	9.1	21.7	12.8	11.9
Diarrhea	0	14.7	9.1	4.3	7.5	7.1
Contusion	3.1	2.9	4.5	21.7	6.8	9.5
Headache	3.1	5.9	13.6	0	6.8	11.9
Nasopharyngitis	3.1	8.8	2.3	13.0	6.0	9.5
Pain In Extremity	0	11.8	4.5	8.7	6.0	4.8
Arthralgia	3.1	8.8	4.5	4.3	5.3	0

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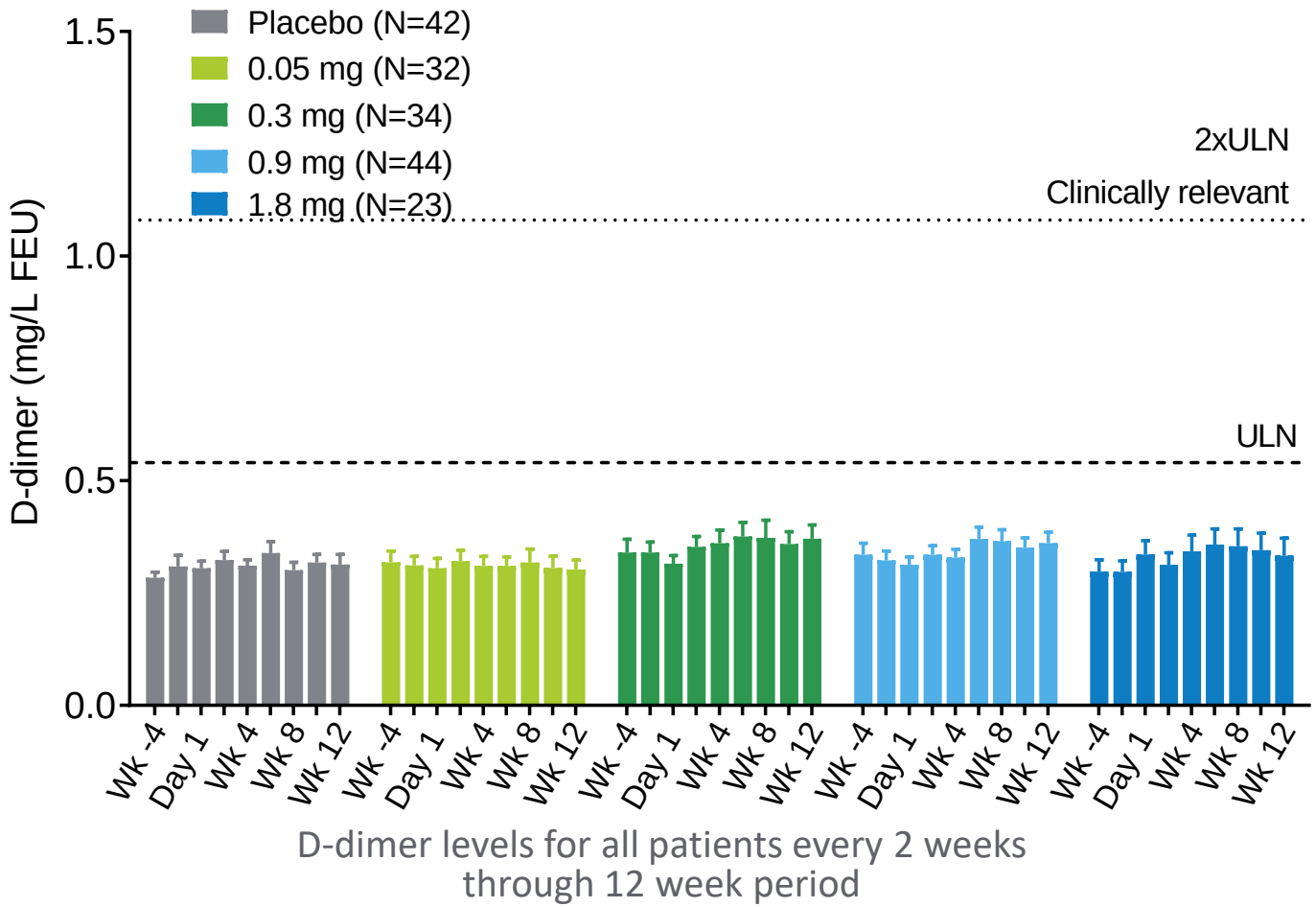
Data are the percent of patients. Safety Population (N=175)

ZGN-1061 D-dimer Profile in Proof-of-Concept Trial



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

- No meaningful elevations in mean D-dimer concentrations across the dosing groups compared to baseline or placebo
- No notable changes in markers of coagulation or other CV safety signals
- 1.8 mg beloranib resulted in a population increase (approximately double) in D-dimer values in retrospective testing of Week 12 samples

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Data are mean ±SE for the safety population (N=175). 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
Plot excludes aberrant values from 2 timepoints due to blood processing issues (024-027 Week 10=7.14; 086-015 Week 12=2.24); the plot excludes D-dimer elevations associated with confirmed AEs of: hand fracture (placebo), gout (0.3 mg), synovial rupture (1.8 mg). Even with inclusion of these confounded values, the mean values are well below the ULN

ZGN-1061 Next Steps

- **Reviewing comprehensive data sets with diabetes/NASH KOLs and potential partners**
- **Important progress made toward addressing the FDA Clinical Hold:**
  - Received FDA Type A meeting minutes to previously announced clinical hold
  - FDA acknowledged newly developed *in vitro* assays of human plasma coagulation and tissue factor expression qualitatively differentiate ZGN-1061
  - Working with FDA to translate *in vitro* data and confirm relevant safety margins in an *in vivo* model
  - Exploring a second IND in a population with higher unmet medical need
  - Company expects to provide an update on development plans by end of 3Q 2019
- **Presented full results of the Phase 2 clinical trial at ADA 2019**

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; doctors have no clear therapeutic options**

ZGN-1258 Summary

- **Unexpected finding observed in long-term toxicology studies**
  - Degeneration and other anomalies in muscle tissue from 4- and 6-month rodent studies
  - Observed in different degrees in both vehicle and all dose arms; finding more pronounced at higher doses
- **Finding never observed previously, specific to ZGN-1258**
  - Not seen in prior ZGN-1258 rodent studies
  - Not seen in any other species with ZGN-1258
  - Not seen in any other Zafgen MetAP2i program in any long-term toxicology study
- **Plan to file an IND suspended while finding is investigated**
- **Company will provide an update at a later time, if warranted, following further evaluation**

PWS Commitment Continues

- *PATH for PWS* natural history study collaboration continues
- Study being conducted in collaboration with the Foundation for Prader-Willi Research (FPWR) and National Organization for Rare Disorders (NORD)
- *PATH for PWS* designed as 4 year / 500 participant non-interventional natural history study
- Enrollment kicked off at FPWR annual conference in October; overenrolled as of June 2019

PATH for PWS™

Paving the way for Advances in Treatments & Health for PWS

ZGN-1345 – Oral, Liver-Focused MetAP2 Inhibitor

- ZGN-1345 advanced to development candidate status in 4Q 2018
- Orally dosed MetAP2i; expected once daily dosing
- High concentrations in the liver; minimal to no detectable exposure systemically
- High MetAP2 levels strongly correlated with more severe outcomes in advanced liver disease
- Positive early data in multiple nonclinical liver disease models with high unmet medical need; further nonclinical studies ongoing

Pathway Platform

Purpose

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

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