



Investor Overview

March 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 in 2Q on work with FDA to address clinical hold
- **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
- **December 31, 2018 cash position of \$118M; 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 2040¹



≥50% of patients have uncontrolled A1C, despite multiple approved treatments available²



In the US, every five minutes 14 adults are newly diagnosed and 2 people die of diabetes-related causes³

Multiple Co-Morbidities; Evolving Guidelines



High incidence of co-morbidities:

- >75% obese⁴
- >70% cardiovascular diseases⁴
- >22-70% NAFLD/NASH⁵
- >35% renal disease⁶

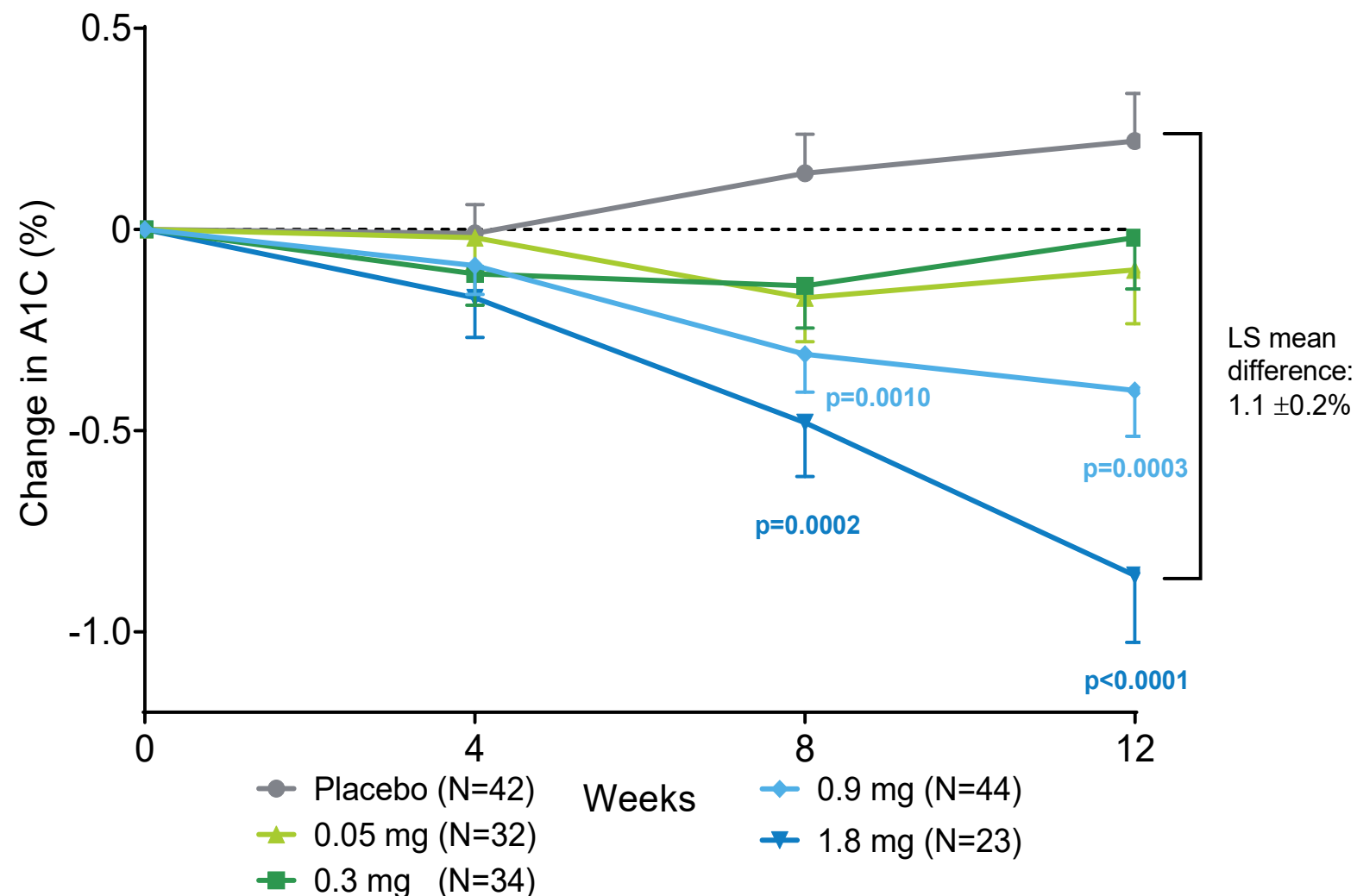


New 2018 ADA/EASD guidelines are patient-centric, driven by co-morbidities, vs previous algorithms that prioritized generics regardless

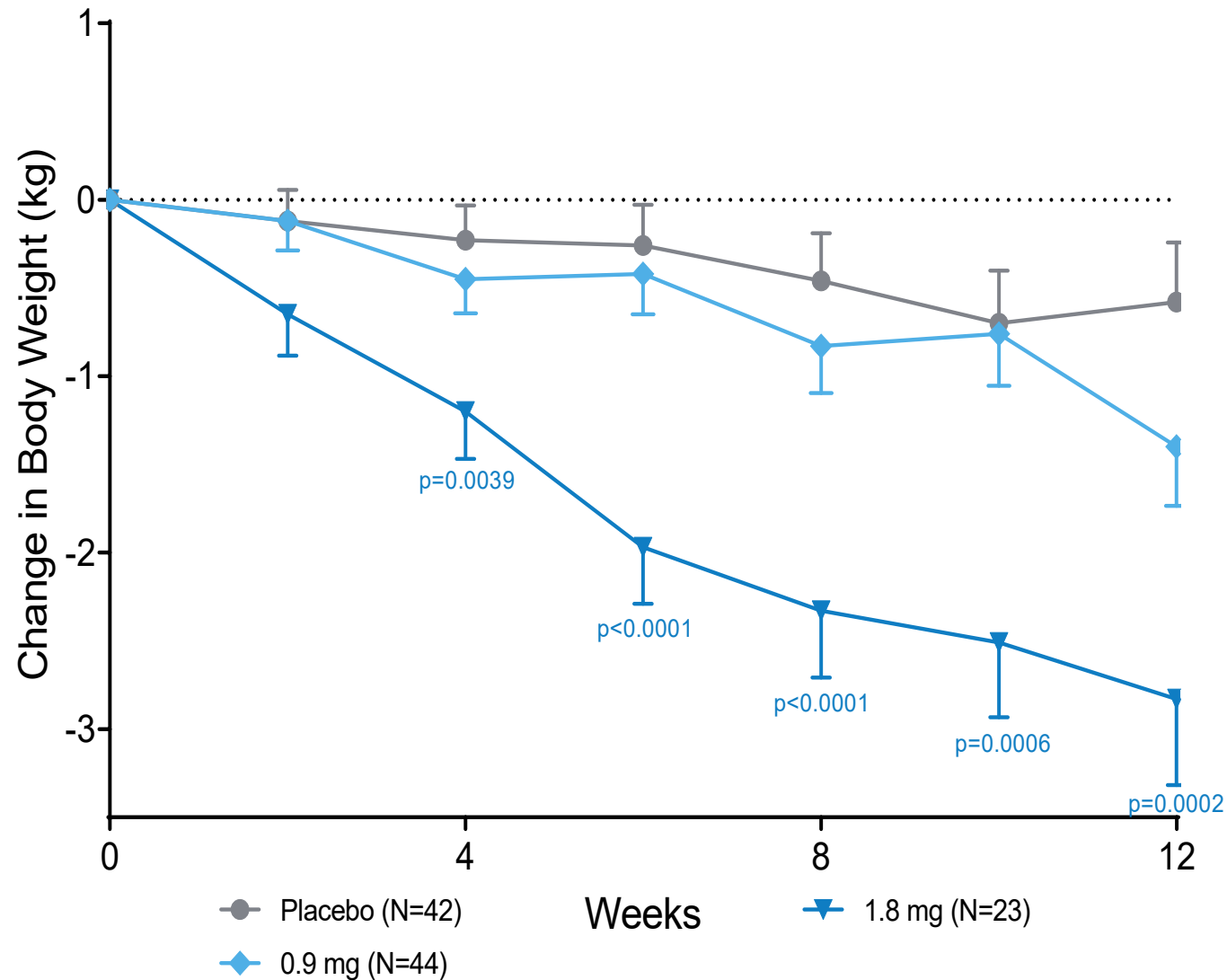
Type 2 diabetic market dynamics include increasing focus on: getting A1C to goal (more effective single agents, combination therapy w/ complementary agents) and positive effects ‘beyond A1C’ that address co-morbidities

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



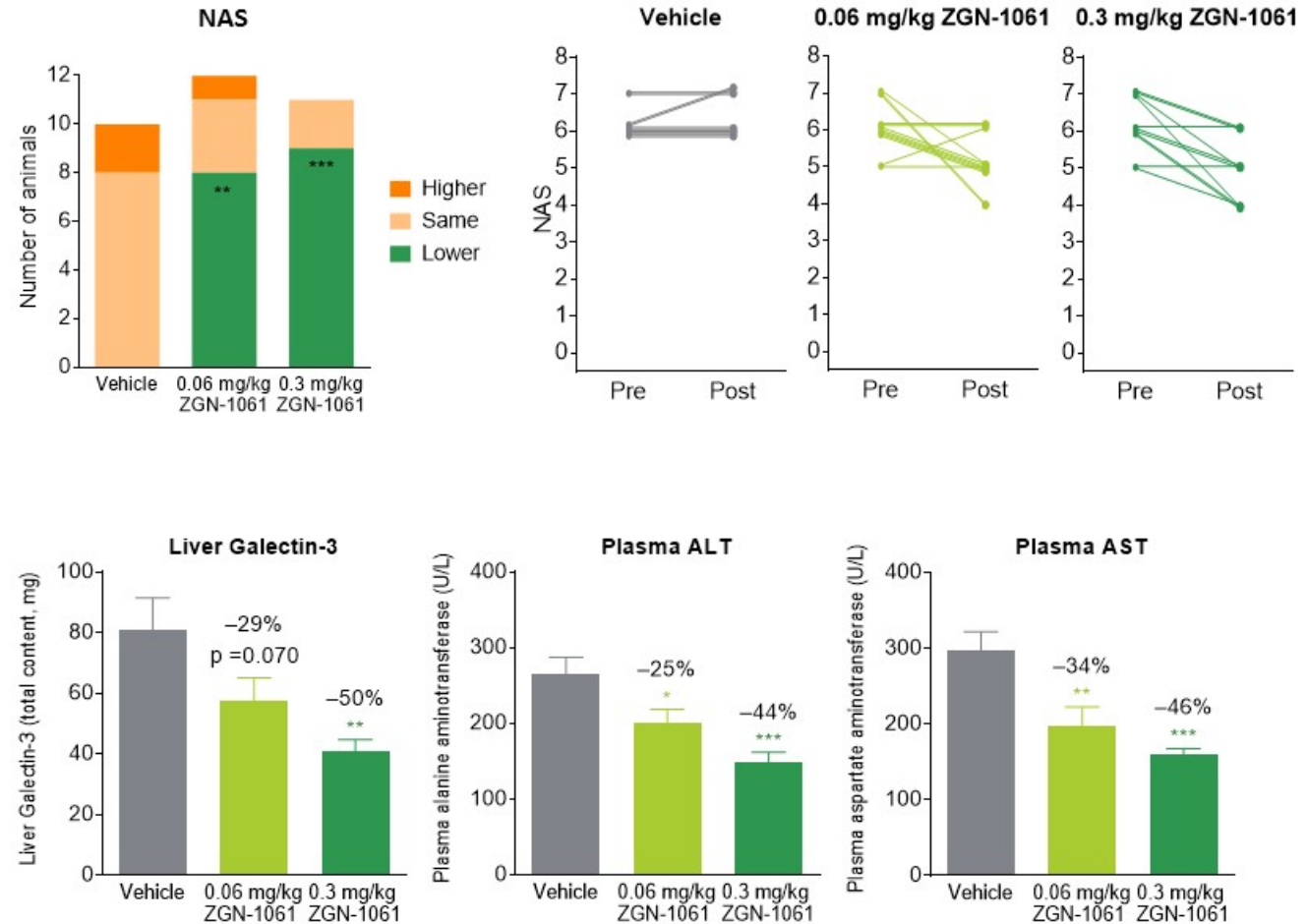
ZGN-1061 Weight Lowering Efficacy in Proof-of-Concept Trial



- 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

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



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 expected¹

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

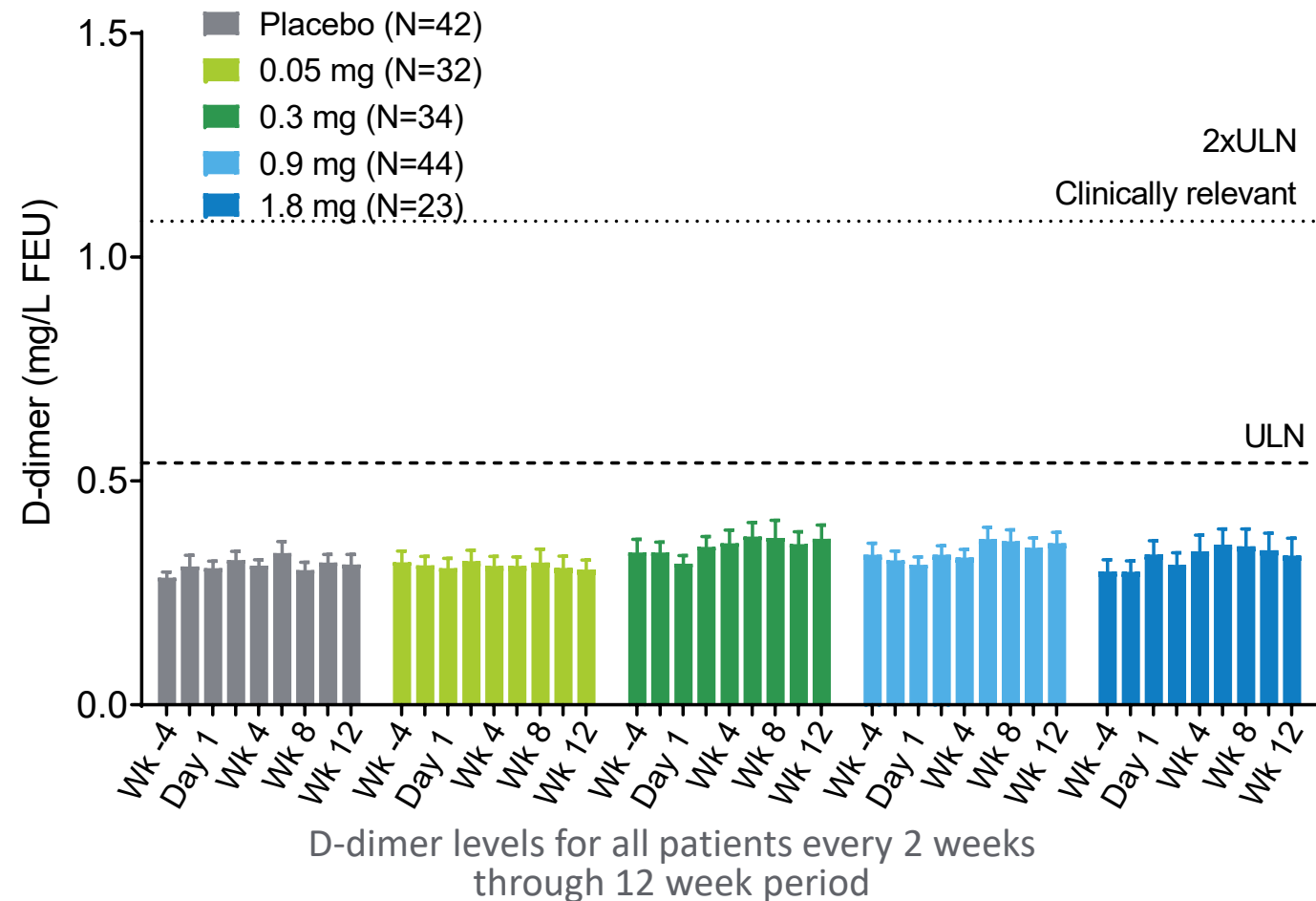
ZGN-1061 Safety / Tolerability in Proof-of-Concept Trial (n=175)

- 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 \geq 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

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



- 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 belorandib resulted in a population increase (approximately double) in D-dimer values in retrospective testing of Week 12 samples

ZGN-1061 Next Steps

- **Reviewing comprehensive data sets with diabetes/NASH KOLs and potential partners**
- **Important progress made toward addressing the FDA Clinical Hold:**
 - Development of new, more sophisticated *in vitro* assays of human plasma coagulation using endothelial cells and assessment of endothelial cell surface expression of tissue factor
 - Working with experts to gain perspective of animal models of thrombosis, and re-evaluation of available animal data
 - Compilation of full safety data from the recently completed Phase 2 proof-of-concept trial
 - Company expects to provide update in 2Q 2019
- **Submitting abstracts to present full results of the Phase 2 clinical trial at upcoming medical meetings in 2019**

Prader-Willi Syndrome



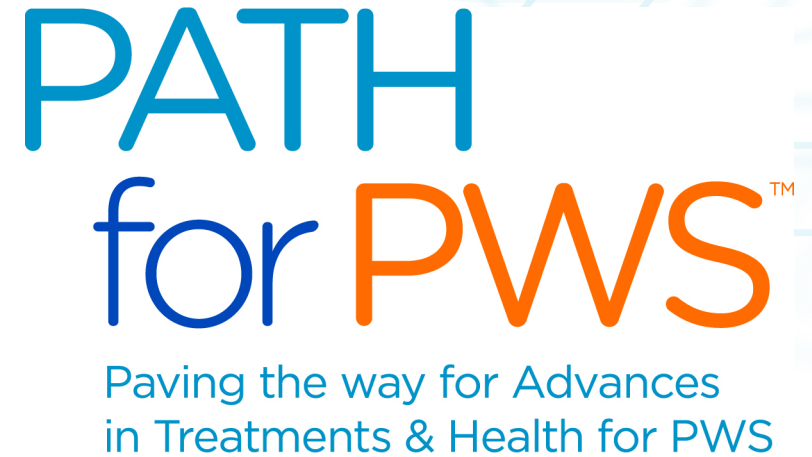
- **Approximately 200,000 patients worldwide (~1:40,000)**
 - Most common genetic cause of life-threatening obesity
- **Characterized by unrelenting pathologic hunger (hyperphagia), and a very low basal metabolic rate**
- **Hyperphagia dominates thought processes**
 - Individuals struggle with concentration, 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; >400 enrolled as of March 2019



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