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Leerink Conference
Feb 15, 2018

Disclaimers

Forward Looking Statements

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.

Investment Highlights

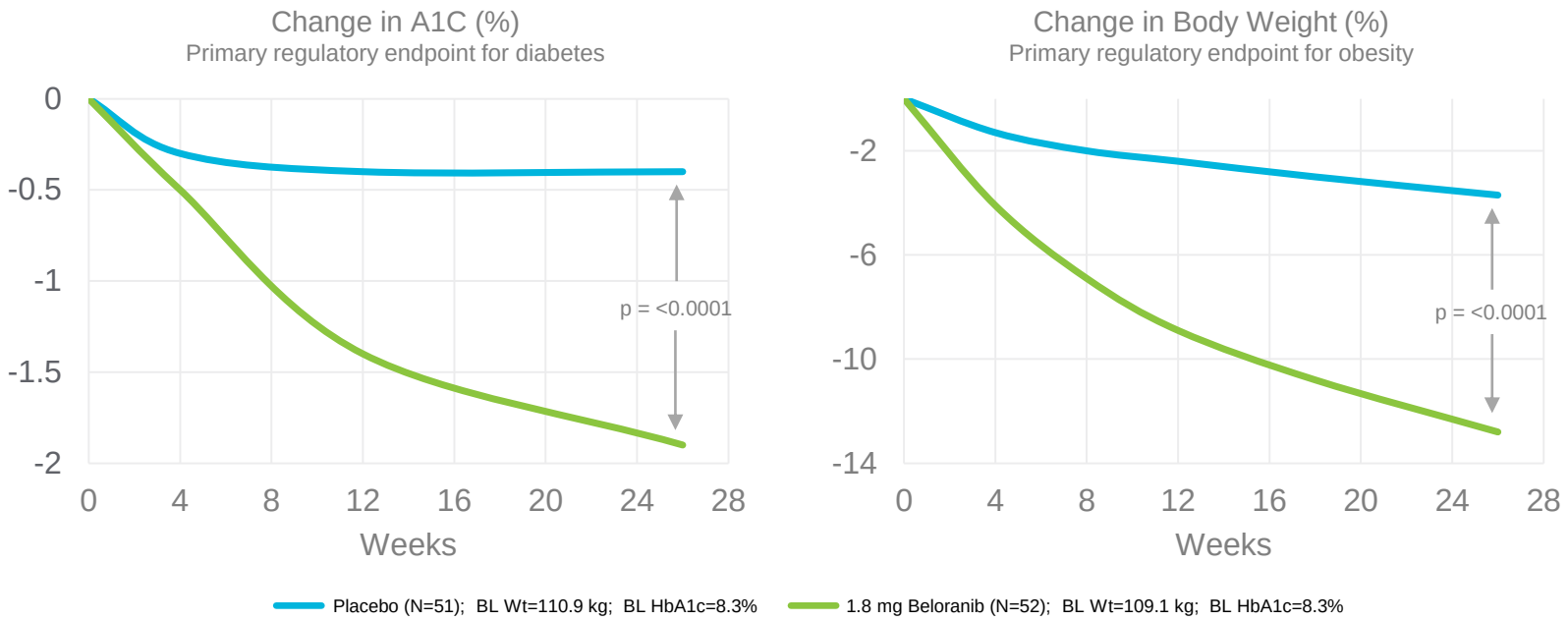
- **A clinical stage biopharmaceutical company with a pipeline of novel therapies for treatment of metabolic diseases with high unmet need**
- **Proprietary, novel MetAP2 biology platform**
  - Clinically validated target; prototype inhibitor demonstrated best-in-field efficacy
  - New chemistry provides improved safety profile, new physical properties that enable development of multiple differentiated assets
- **ZGN-1061 for difficult-to-control type 2 diabetes**
  - Potential to deliver clinical superiority vs insulin in Type 2 diabetes ($15B insulin market segment)
  - Ph 2 proof-of-concept trial ongoing; results expected mid-year 2018
- **ZGN-1258 for rare metabolic diseases; returning to Prader-Willi syndrome first**
  - Expected to begin IND-enabling studies 1Q 2018; Ph 1 in 4Q 2018
  - Company will leverage prior PWS experience to facilitate rapid advancement
- **Additional assets in development leveraging proprietary MetAP2 biology insights**
- **December 31, 2017 cash position of just over $100M; runway into 2H 2019**
- **Management team experienced at delivering value to patients and shareholders**

Management Team

 **Jeffrey Hatfield** *CEO*	 **Thomas E. Hughes, Ph.D** *President & CSO*	 **Patricia Allen** *CFO*	 **Dennis D. Kim, M.D., M.B.A.** *CMO*	 **James E. Vath, Ph.D.** *Head of Discovery & Development*
vitae Pharmaceuticals Bristol-Myers Squibb	NOVARTIS SANDOZ a Novartis company	Alnylam PHARMACEUTICALS Alkermes Deloitte & Touche	AMYLIN OREXIGEN EnteroMedics	Genetics Institute PRAECIS MILLENNIUM
Glucophage® Metformin Hydrochloride PRAVACHOL (pravastatin sodium) 40 mg tablets	Galvus vildagliptin		Byetta® (exenatide) injection Once-weekly BYDUREON® exenatide extended-release for injectable suspension 2 mg	BeneFix® Coagulation Factor IX (Recombinant) Room Temperature Storage *BeneFix was approved February 11, 1997. INFUSE®

First MetAP2i Validated Target and Established Best-in-Field Efficacy

- **MetAP2i efficacy unprecedented on metabolic disease regulatory endpoints**

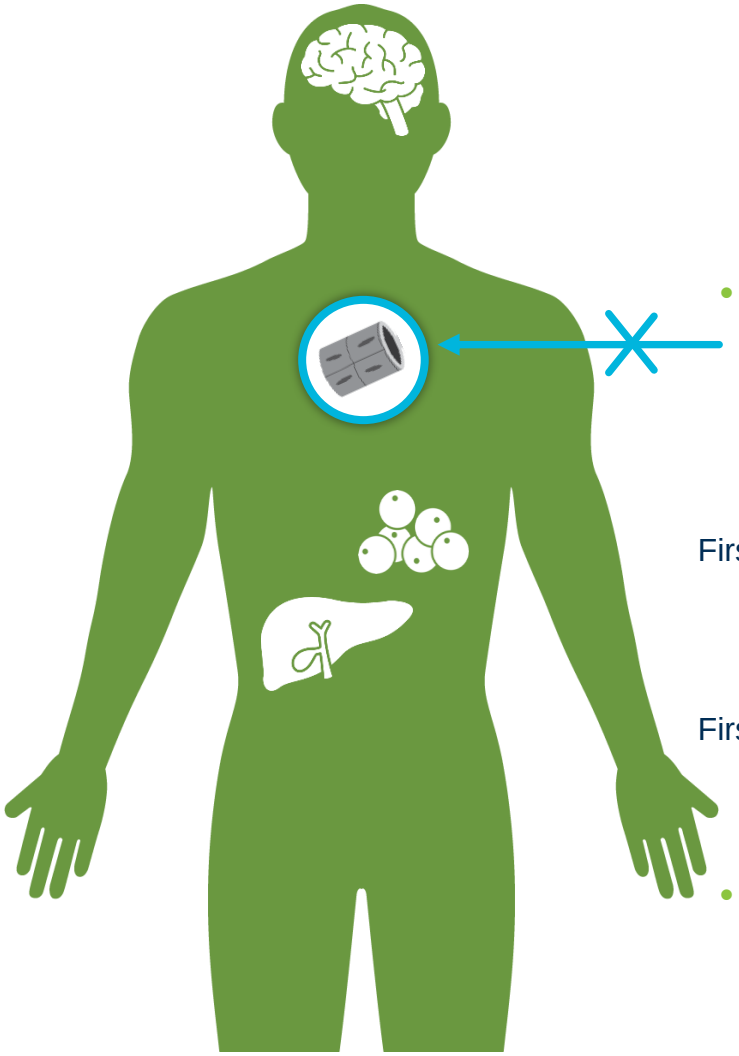


- **MetAP2i efficacy unprecedented with pan-metabolic parameters**

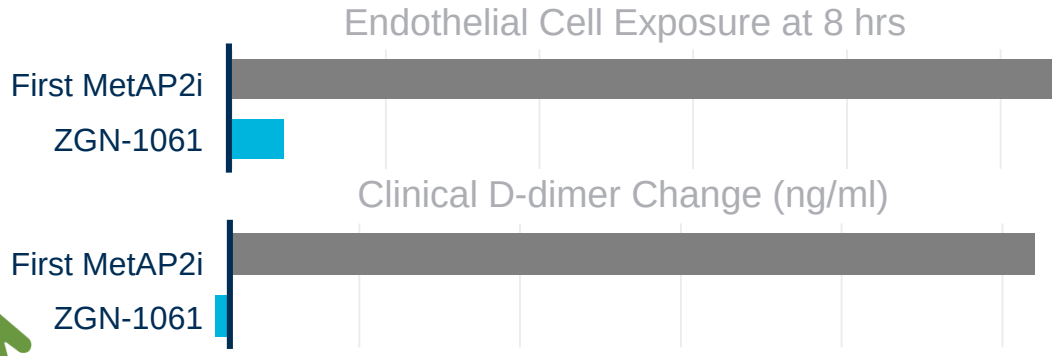
▲ HDL	▼ Blood pressure	▼ Hunger	▼ Food intake
▼ LDL	▼ Inflammation (CRP)	▼ Leptin	▼ Body comp
▼ Triglycerides	▼ Waist-to-hip	▲ Adiponectin	▼ Liver fat

- **Zafgen has proprietary knowledge of complex MetAP2 biology pathway and clinical translation; further enhanced by extensive intellectual property estate**

New Chemistry Enables Tissue Targeting; Improves Safety, Differentiates Pipeline

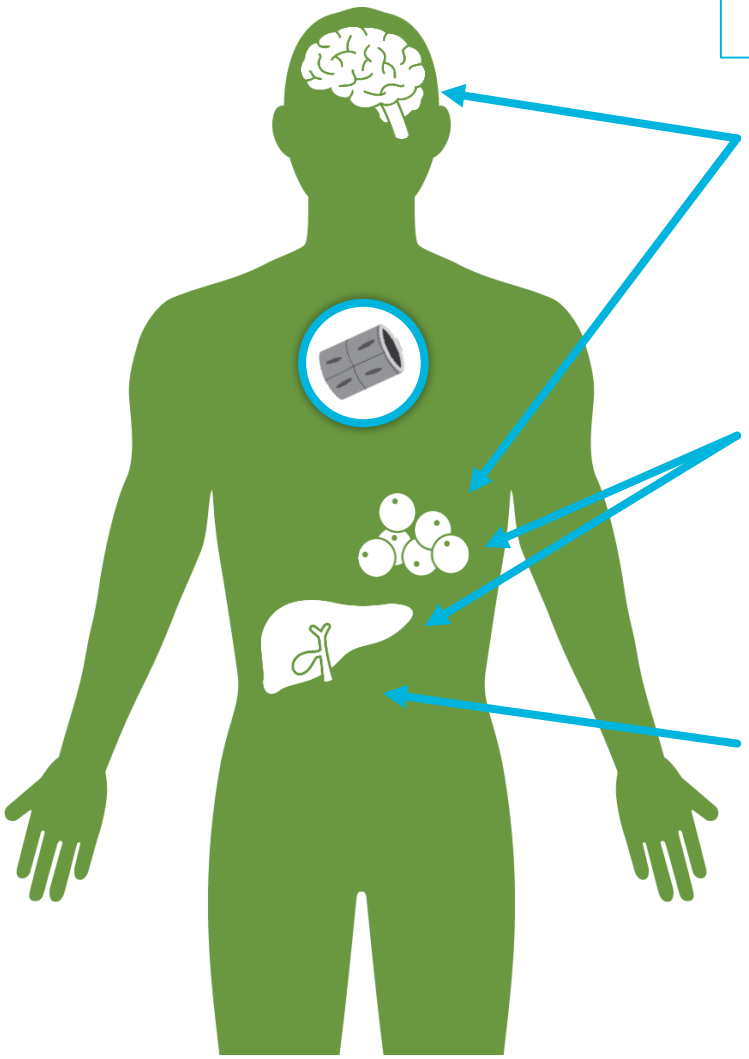


- **New chemistry enables differentiated tissue distribution, significantly improving safety profile**
  - First MetAP2i safety limitation driven by prolonged exposure in endothelial cells, where it readily distributed into and became trapped for >24 hours
- **<u>All</u> current pipeline compounds minimize endothelial cell penetration, eliminate trapping phenomenon**



- **Greater than 100x safety margin for endothelial effect with new chemistry**

New Chemistry Enables Tissue Targeting; Improves Safety, Differentiates Pipeline



Tissue targeting know-how also creates potential for clinically differentiated efficacy:

1. **ZGN-1258**: CNS, adipose, liver distribution
   - Efficacy includes effects on dysregulated hunger control centers in the brain
   - **Prader-Willi syndrome** → HIAO, leptin$^{-/-}$, etc.

2. **ZGN-1061**: adipose, liver distribution
   - Efficacy driven by effects on peripheral insulin sensitivity, glucose utilization and storage
   - **Type 2 diabetes** → option vs insulin and / or patients at diabetes-obesity-NASH intersection

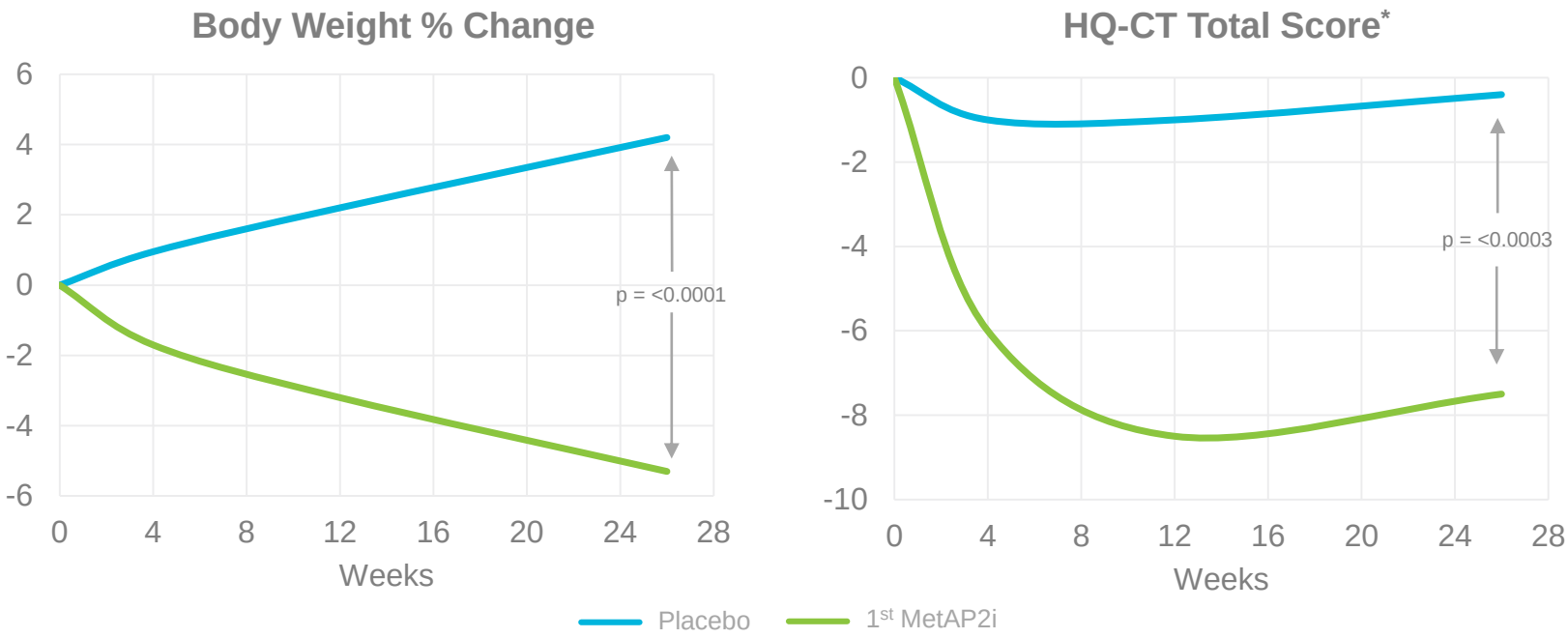
3. **Pipeline**: liver distribution (oral)
   - Efficacy driven by effects on hepatic glucose uptake, insulin action, inflammation
   - **Liver indication TBD** → NASH, ASH, HCC, etc.

Prader-Willi Syndrome

- **Approx. 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 w/ 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 both co-primary endpoints in prior Ph 3 clinical experience**

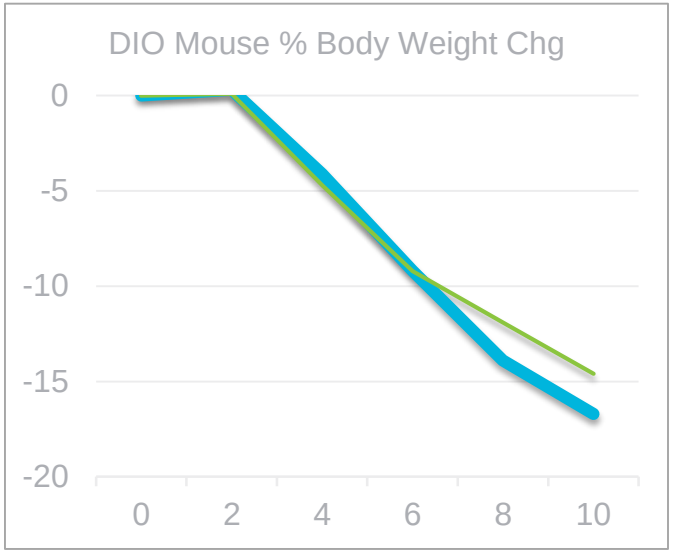


- **Well tolerated; profile observed as generally equal to placebo**
- **Endothelial cell issue arose halting progression of first MetAP2i**

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

ZGN-1258 Preclinical Profile

Endpoint	ZGN-1258	1st MetAP2i
MetAP2 Enzyme IC_{50}, nM	6.5	4.0
Mouse DIO Efficacy (10 Day - 0.3mpk - % BW loss)	17%	15%
Mouse ob/ob Efficacy Model of Obesity and Hyperphagia	Robust weight loss, reduced food intake	Robust weight loss, reduced food intake
Rat DIO Efficacy (10 Day - 0.3mpk - % BW loss)	6.8%	6.5%
Dog Pharmacokinetics	Rapid Clearance (<8hr)	Slow Clearance (>24hrs)
Dog Thrombosis	>100x margin	<5x margin
Core Patent Expiration	2036	2024



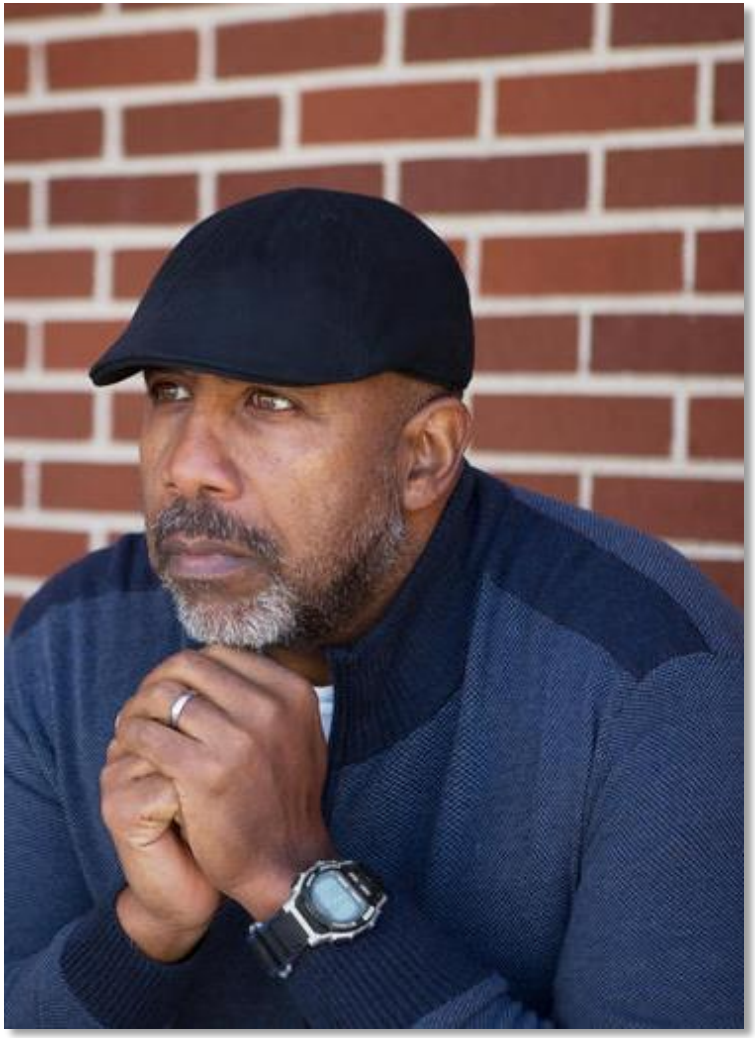
Natural History Study Plan

- **Lesson learned from prior experience – a robust understanding of PWS natural history and medical complications important**
  - Provides context for benefits of treatment and any adverse events
  - Study requires GCP quality with pre-defined objectives
- **Company plans to conduct a formal natural history study; expects to partner with patient advocacy groups and FDA / ORD on design**
  - Patient advocacy groups have already begun initial discussions with FDA; have indicated willingness to team with Zafgen
- **Study expected to initiate mid-year 2018; run in parallel with ZGN-1258 clinical development**

ZGN-1258 Advancing Towards Clinic

- **ZGN-1258 advancing into IND-enabling studies 1Q 2018**
  - -1258 extensively vetted preclinically; size, scope and duration of completed preclinical studies exceeds that typically seen for Ph 1 initiation
- **Ph 1 expected to start in 4Q 2018**
- **Company expects to leverage extensive experience in PWS to enhance / accelerate ZGN-1258 clinical development**
  - Operational experience in clinical development
  - Experience with validated patient reported outcomes tool developed in-house (HQ)
  - Regulatory experience in US, EU
  - KOL relationships
  - Patient advocacy relationships
- **The Foundation for Prader-Willi Research (FPWR) has recently developed a registry with ~1700 patients, specifically to accelerate clinical trials for promising therapies**

ZGN-1061 for Type 2 Diabetes

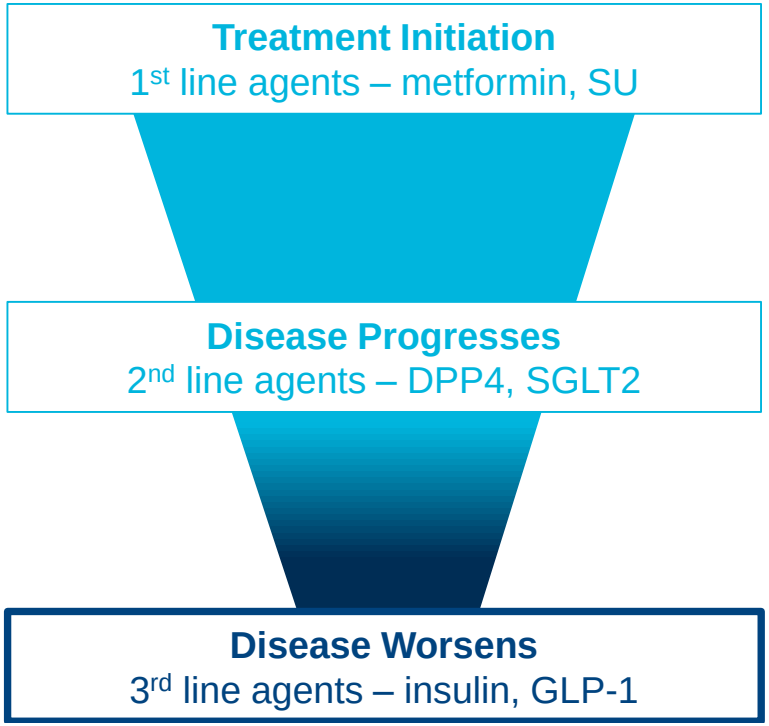


Target Patient Population:

- **Takes metformin, DPP4 and/or SGLT2**
- **Blood sugar, other metabolic values still high; diabetes not under control**
  - HbA1c 8.4%
  - Weight 265 lbs
  - Blood pressure 155 / 90 mm Hg
  - Total cholesterol 235 mg/dl
- **Doctor suggests insulin may be the next step**

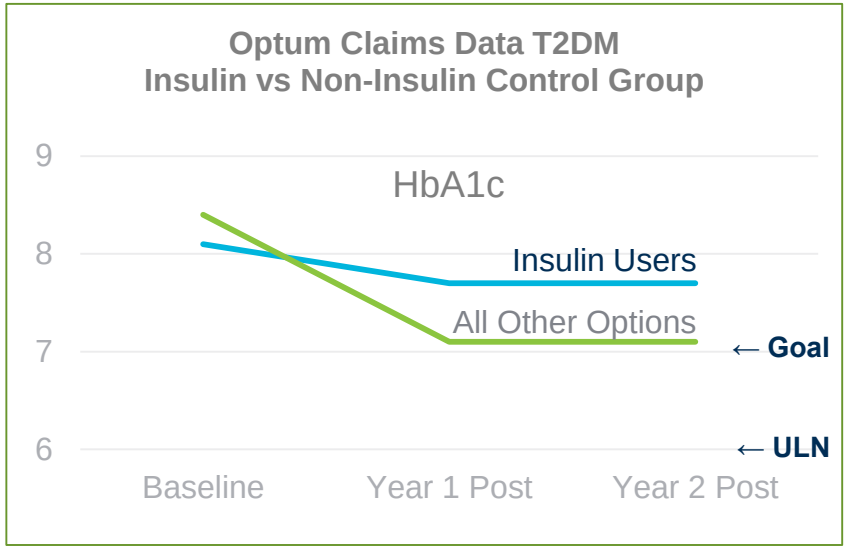
ZGN-1061 Market Opportunity

- **Diabetes among world's largest markets; 425 million people affected globally in 2015; almost 10% of U.S population**



- **$15B annual insulin sales in T2DM**

- However, insulin HbA1c benefit unclear using claims database RWE (Real World Evidence)



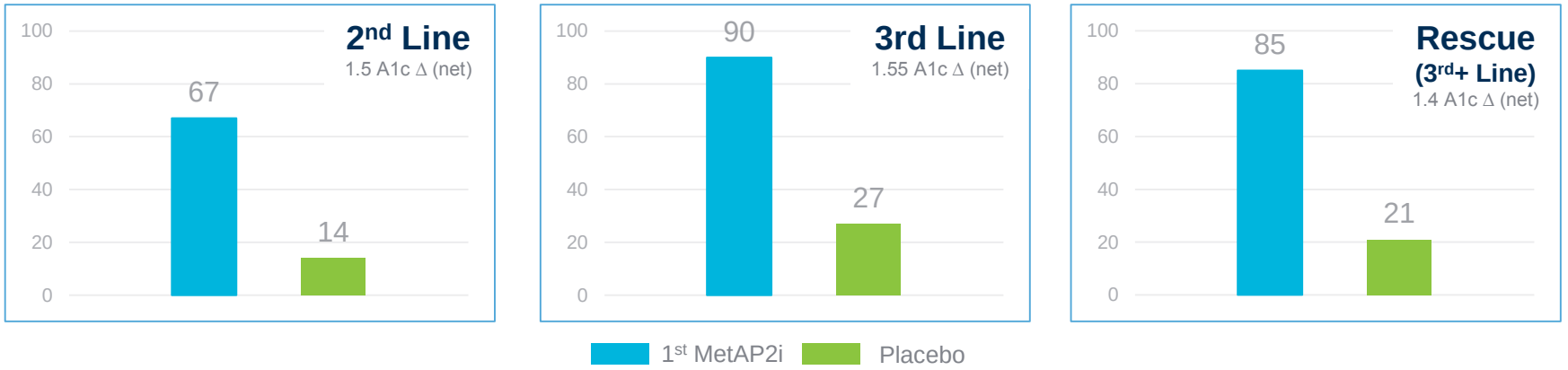
Insulin limitations include: weight gain, hypoglycemia, daily monitoring and injection burden, limited impact on metabolic parameters beyond blood glucose

* ULN – upper limit of normal (HbA1c)

ZGN-1061 Market Opportunity

- **$15B annual insulin sales in type 2 diabetes; typical 3rd line patient complex:**
  - HbA1c > 8.0
  - Obese to morbidly obese
  - Pan-metabolic dysregulation (LDL, Trig's, BP, NASH)
- **Opportunity for novel therapeutic that offers:**
  - Significant HbA1c effects, in 3rd line setting
  - Additional pan-metabolic benefit

% Patients achieving goal of < 7.0 HbA1c after 26 weeks treatment with 1st MetAP2i



ZGN-1061 Phase 1 Results

Ph 1a (n = 39 normal healthy volunteers)

- **Single ascending dose trial with doses from 0.2mg to 4.8mg** (6 cohorts, 3:1 vs placebo)
- **All doses generally safe and well tolerated**
  - AE's equivalent to placebo; no withdrawals due to AE; no SAE's
  - No safety signals

Ph 1b (n = 29 obese healthy volunteers)

- **Multiple ascending dose 28 day trial from 0.2mg to 1.8mg** (3 cohorts, 3:1 vs placebo)
- **All doses generally safe and well tolerated**
  - AE's equivalent to placebo; no withdrawals due to AE; no SAE's
  - No safety signals
- **Initial indication of efficacy**
  - Modest weight loss; trends for improvement observed in multiple metabolic measures: LDL-C, food intake, waist circumference, adiponectin, leptin, c-reactive protein

ZGN-1061 Ph 2 Proof-of-Concept

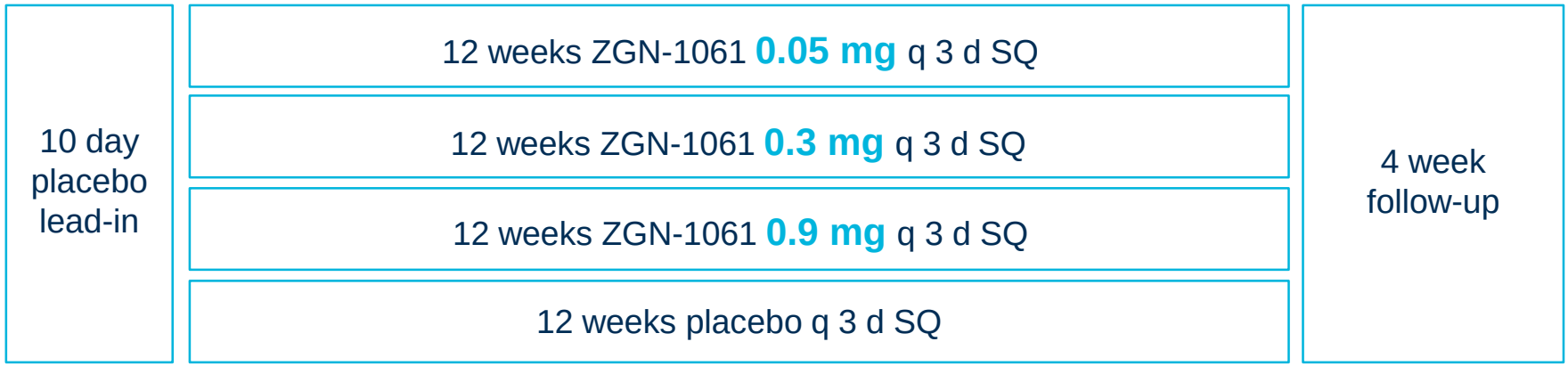
- **ZAF-1061-201 is a randomized, double-blind, placebo-controlled trial of patients with type 2 diabetes with HbA1c between 7.0–11.0% and BMI ≥ 27**
- **ZAF-1061-201 clinical trial fully (over) enrolled at 137 patients (vs 120 target)**
  - Enrollment rate accelerated significantly in final weeks of trial enrollment
- **Patient characteristics**

Average Age	54 years
Males / Females	53% / 47%
Average HbA1c	8.7%
Average Fasting Plasma Glucose	199 mg/dl
Average BMI	37 kg/m^2

Approximately half of study participants at 3rd line +

- **Primary endpoints**
  - HbA1c
  - Safety and tolerability
- **Secondary endpoints**
  - Glycemic control biomarkers
  - Weight loss
  - Cardiometabolic and inflammatory biomarkers

ZGN-1061 Ph 2 Proof-of-Concept

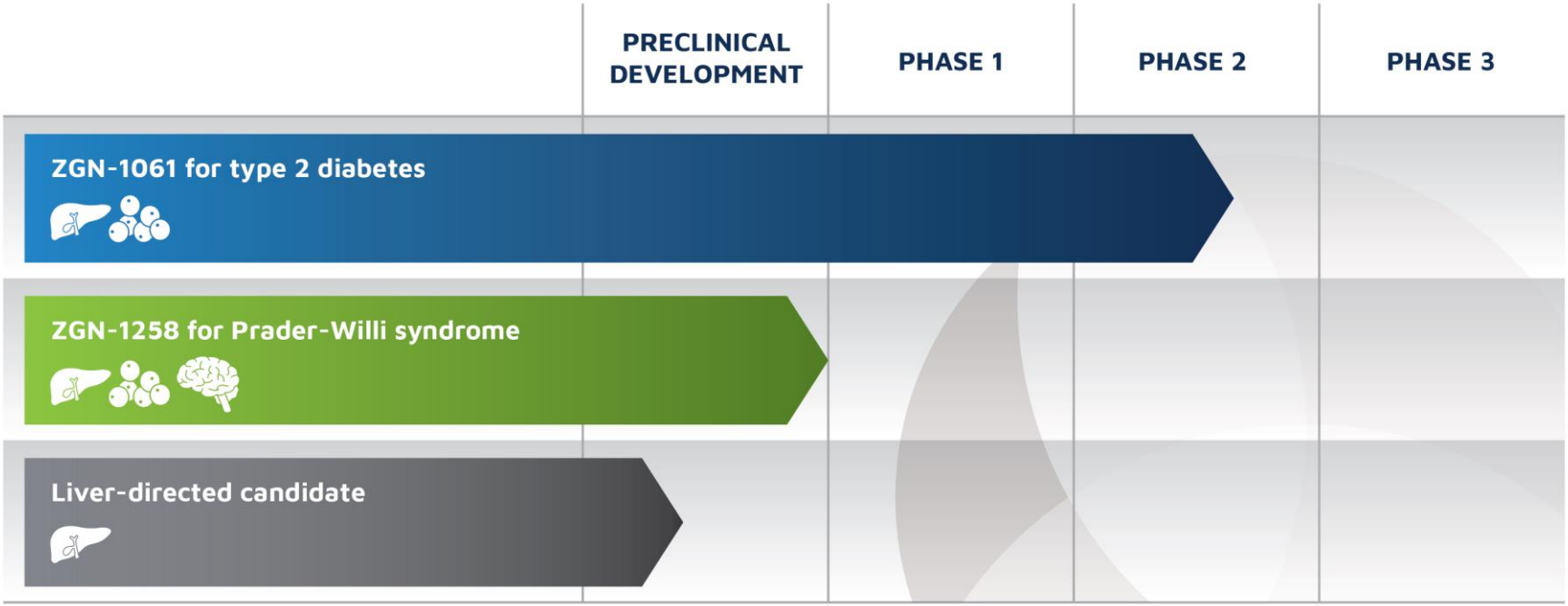


Expectations for trial:

- **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
  - Leading indicator measures – fasting plasma glucose, lipids, adiponectin, CRP will aid in establishing dose response curve

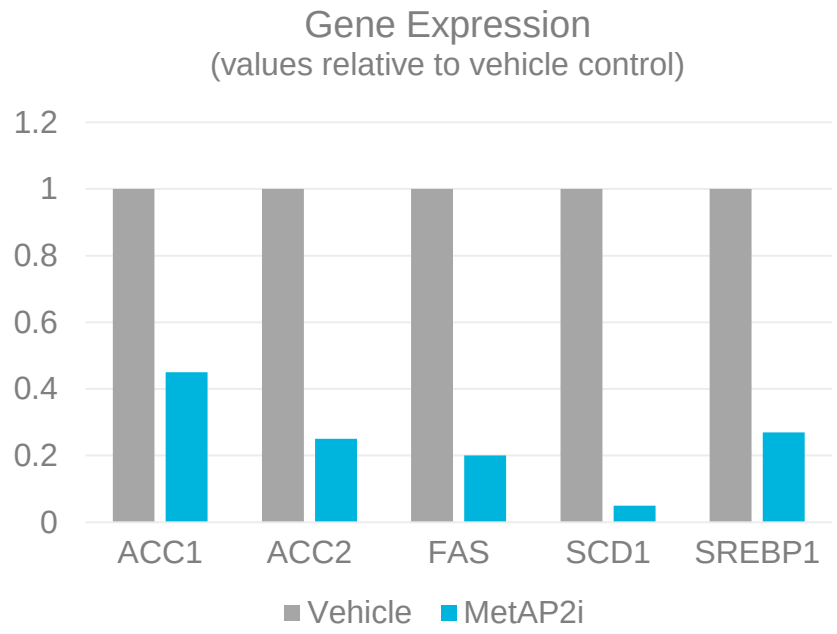
Full topline data expected mid-year 2018

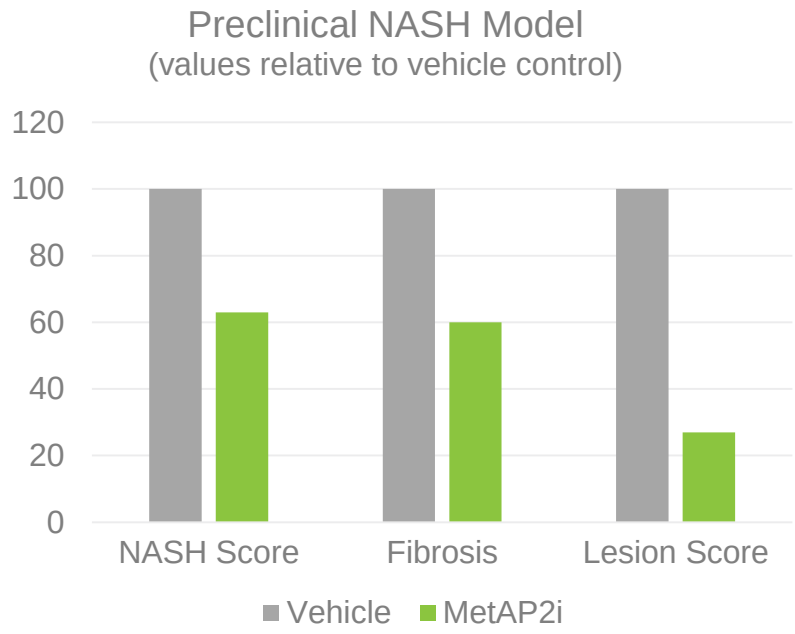
MetAP2i Pipeline



MetAP2i Has Potential for Liver Disease

- **MetAP2i biomarker effects in the liver demonstrate potential for significant impact on NASH, ASH and / or hepato-cellular carcinoma (HCC)**
  - Profound effect on genes responsible for fat synthesis, fat metabolism and inflammatory processes
  - Significant impact on NASH score, fibrosis progression and lesion formation





- **2018 goals are selection of development candidate and first indication**

Intellectual Property

- **Broad MetAP2 pathway biology (issued & pending claims)**
  - Obesity
  - Diabetes
  - Hyperphagia
  - NAFLD/NASH
  - Hepatobiliary
  - Renal
  - Age-related disorders

- **ZGN-1061**
  - Issued patent includes composition genus and specific compound, expires 2036
  - Pending PCT (worldwide) application covering methods of treating e.g., diabetes, NASH, obesity, etc.
  - Pending U.S. patent application covering treatment of T2DM using 1061 (genus and compound)
  - Additional method of use, crystalline forms, and composition patent applications pending (if issued will expire ~2038)

- **ZGN-1258**
  - Pending U.S. application to composition of matter
  - Pending PCT application to composition of matter and methods of use, including Prader-Willi syndrome
  - Pending U.S. application to additional methods of use/indications

Pipeline Milestones

Program	Milestones	Timing
ZGN-1061 for type 2 diabetes	• Ph 2 proof-of-concept data • IND allowance for future clinical trials *	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

- **Just over $100M of cash and cash equivalents as of December 31, 2017**
- **Operating runway into 2H 2019; includes multiple value inflection milestones**

* Current Ph 2 trial being conducted in Australia and New Zealand, allowed company to accelerate time to data ~6 months and decrease trial cost ~40% due to Australia R&D incentives

Company Summary

- **Proprietary, novel MetAP2 inhibition pathway platform**
  - **ZGN-1061** for difficult-to-control type 2 diabetes
  - **ZGN-1258** for rare metabolic diseases; returning to Prader-Willi syndrome
  - Additional pipeline assets in development
- **Multiple value inflection points spread throughout 2018**
- **December 31, 2017 cash position of just over $100M; runway into 2H 2019**
- **Management team experienced at delivering value to patients and shareholders**

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Pathway Platform *Purpose*

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