ZAF-1061-101
Clinical Trial Results

May 4, 2017

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Introduction to ZGN-1061

Tom Hughes, Ph.D., President and Chief Executive Officer

ZGN-1061: A Differentiated Profile

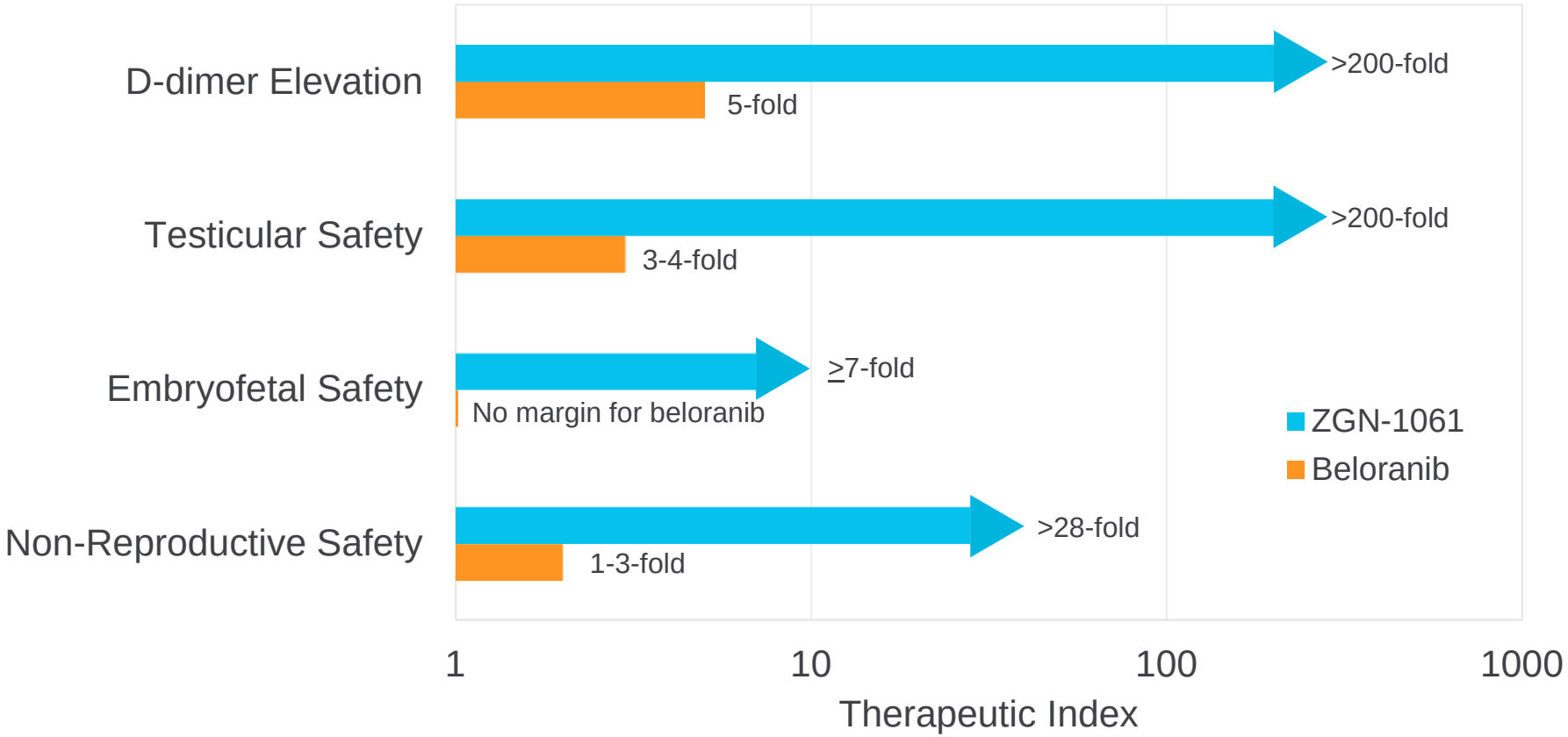
- Phase 1 clinical trial showed that it was well-tolerated and safe
- Pharmacokinetic and target engagement profile met our prospectively established criteria
- Weight change supportive of drug effect
- Metabolic parameter changes consistent with MetAP2 inhibitor effects

ZGN-1061 has the expected differentiated profile to support further development

ZGN-1061: Highly Optimized, More Advanced MetAP2i

		Beloranib	ZGN-1061
Efficacy	**Impact on weight loss, glycemic control, CV risk factors**	Fully effective based on pre-clinical and clinical data	Equivalent efficacy based on pre-clinical profile Promising clinical safety and tolerability
Pre-clinical Safety	**Embryofetal development impact**	No margin	Improved margin
	Testicular toxicity	Narrow margin	No impact
	Thrombotic risk surrogate	Narrow margin	Substantial margin
Economics	**Royalties/milestones due**	Up to $22.5M in milestones; single digit royalties	None; Wholly-owned
	Manufacturing	Complex	Simplified
	Patent life	2029-2031	2036+
Opportunity	**Markets**	Orphan indications	Prevalent metabolic indications
	Lead indication(s)	PWS, HIAO	Type 2 diabetes

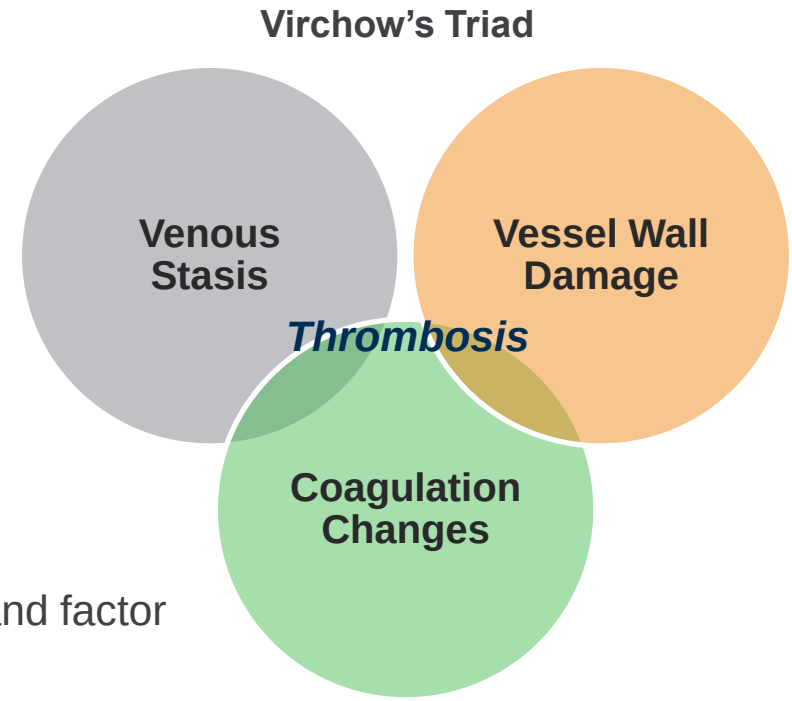
ZGN-1061 has Been Optimized for Markedly Improved Safety Margins* vs. Beloranib in Non-Clinical Studies



*Values represent the ratio of exposures observed or estimated at no observed adverse effect level (NOAEL) doses from animal studies in which endpoints have been observed, relative to known exposures for beloranib (2.4 mg twice-weekly) or clinical exposures for ZGN-1061 (~0.9 mg or lower). Ranges represent the lowest and highest estimated ranges based on male and female animals, where relevant, of all species evaluated. Results are from animals and are not necessarily predictive of human results or results of longer-term studies.

Mechanistic Basis for Improved Safety of ZGN-1061

- No effects of beloranib seen on
  - Platelets or platelet aggregation
  - Neutrophil adhesion or NETs formation
  - Clotting factor levels or function
  - Blood clotting or clot lysis
- Effects of beloranib seen on vessel wall cell function
  - Endothelial cell proliferation slowed
  - Endothelial cell anticoagulant function
    - e.g., PAI-1, thrombomodulin, von Willebrand factor



Striking difference in sensitivity to beloranib vs. ZGN-1061 – correlates with differential sensitivity *in vivo*

ZAF-1061-101 Phase 1 Clinical Trial Results

Dennis Kim, M.D., Chief Medical Officer

ZAF-1061-101 Clinical Trial Design and Demographics

ZAF-1061-101	Single Ascending Dose (SAD)	Multiple Ascending Dose (MAD)
Patient population	Healthy	Healthy, obese
N	39	29
Demographics	90% male; average BMI of 26	76% male; average BMI of 33
Dosing cohorts	0.2, 0.6, 1.2, 2.4, 3.6, 4.8 mg	0.2, 0.6, 1.8 mg
Dosing schedule	Single dose	Twice-weekly dosing for 28 days (8 injections)
Randomization	3:1 (active/placebo)	3:1 (active/placebo)
In-patient treatment	Domiciled days -1 through 4	Domiciled for the majority of the trial for closer safety monitoring: • No exercise allowed • Controlled food intake, including meal challenges

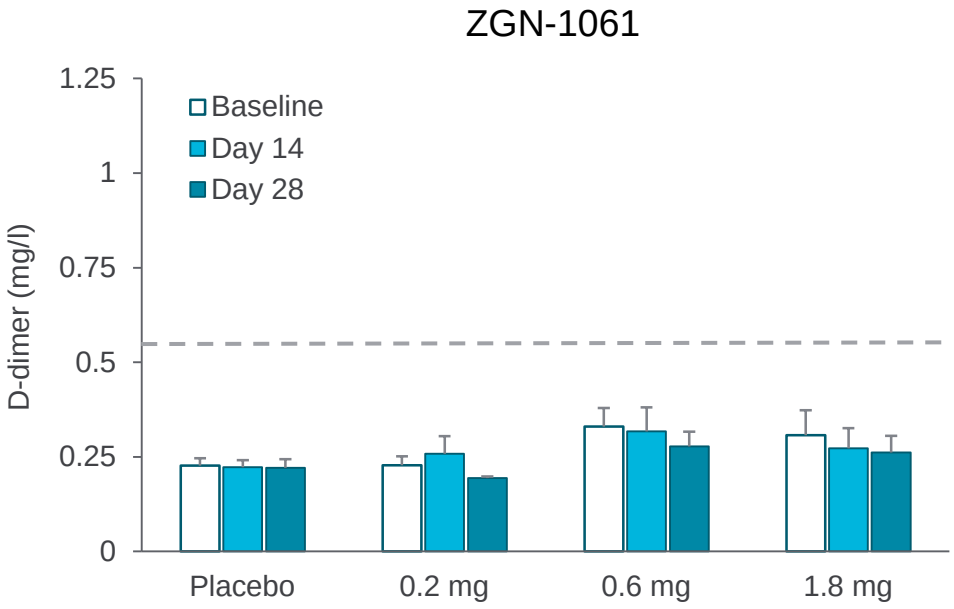
ZAF-1061-101 – Summary of SAD Phase

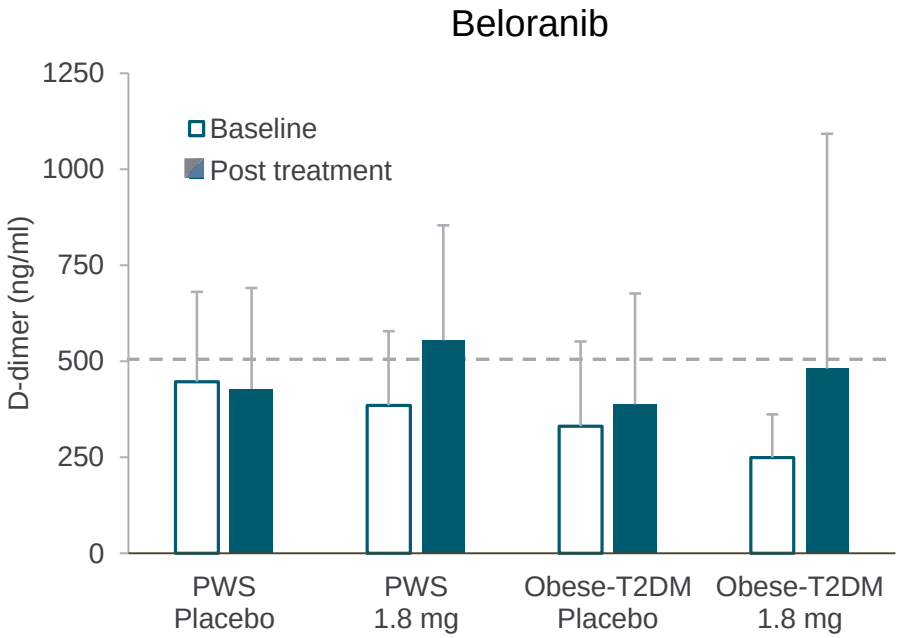
- No safety signals were identified
- Single doses of ZGN-1061 (0.2 mg to 4.8 mg) were well-tolerated
- No noted trends by dose or type of adverse event (AE)
- No serious adverse events (SAEs) or withdrawals due to an AE
  - One moderate event of flank pain (0.6 mg); all other adverse events were mild
- No adverse trends in coagulation related measures, which on average remained within the normal range
- No meaningful changes observed among general safety laboratory measures, blood pressure, heart rate, or electrocardiograms
- Favorable pharmacokinetics
  - Plasma concentrations of ZGN-1061 increased linearly with dose
  - Rapid absorption and a similarly rapid clearance
  - Maximum concentrations occurring within 30 minutes of dosing

ZAF-1061-101 MAD Phase: Safety Summary

- Safe and well-tolerated
  - No serious adverse events (SAEs), no severe adverse events (AEs)
  - No AEs leading to early withdrawal from the clinical trial
  - All AEs were of mild intensity in the MAD phase except one (toothache)
  - Most common side effects were mild gastrointestinal issues (comparable between ZGN-1061 relative to placebo), headache and procedural related irritation
  - No sleep disturbance
- Reassuring thrombosis-relevant data
  - No venous thromboembolisms (VTEs)
  - No D-dimer elevations indicative of the presence of VTEs
  - No meaningful elevations in mean D-dimer concentrations across the dosing groups compared to baseline or placebo
  - No changes in standard coagulation laboratory values

No Group-Wise Increases Observed for ZGN-1061 in D-Dimer Marker that was Impacted by Beloranib

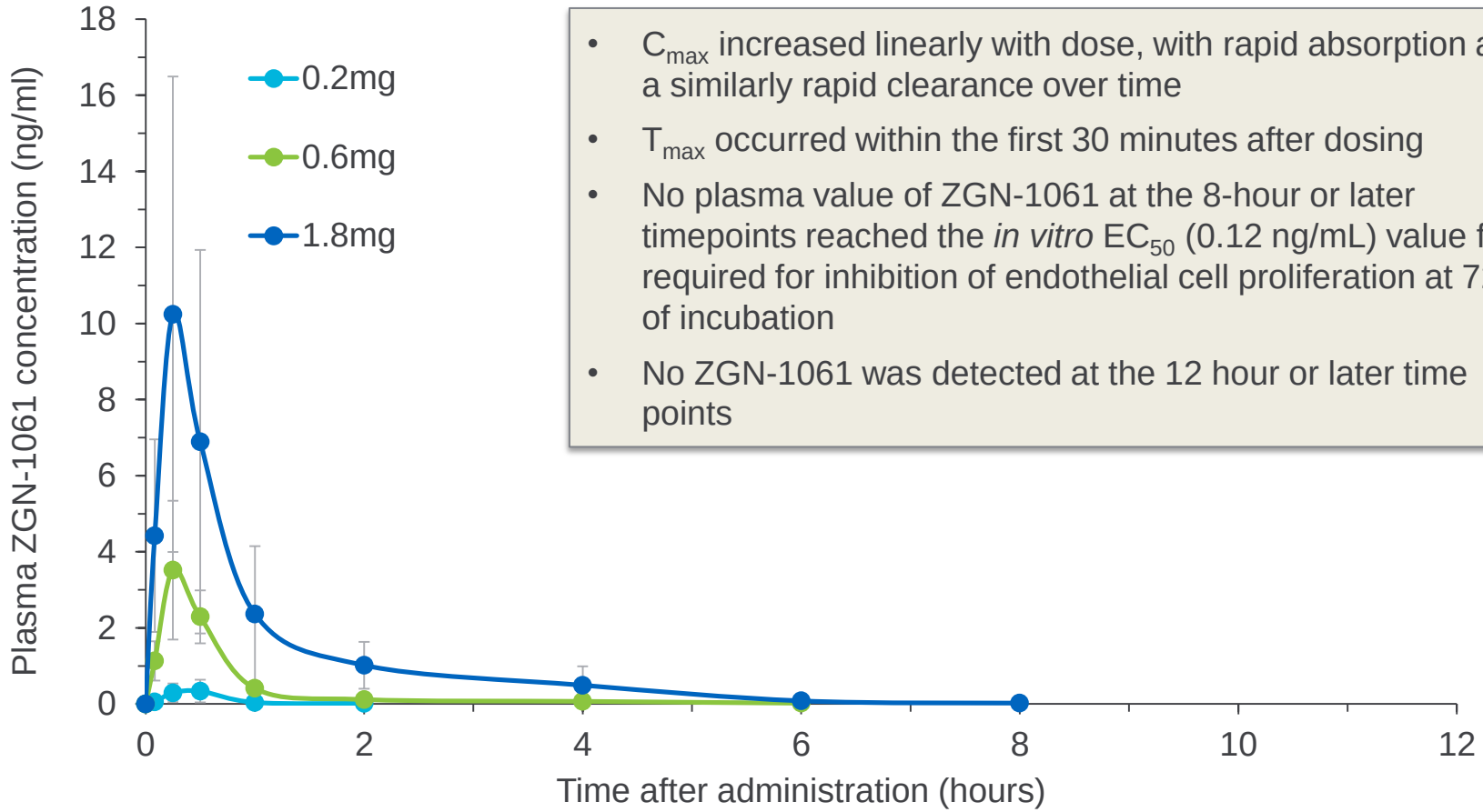




Dashed line indicates the upper limit of normal for the D-dimer assay used for each program

- D-dimer, a fibrin degradation product, is a conventional marker of clotting and becomes markedly elevated during periods of active clot formation and lysis
- Beloranib treatment in humans was associated with elevated D-dimer levels, leading to group-wise elevations
- ZGN-1061 treatment for 28 days was not associated with group-wise D-dimer elevations

ZGN-1061 Pharmacokinetic Profile Meets Prospectively Established Criteria

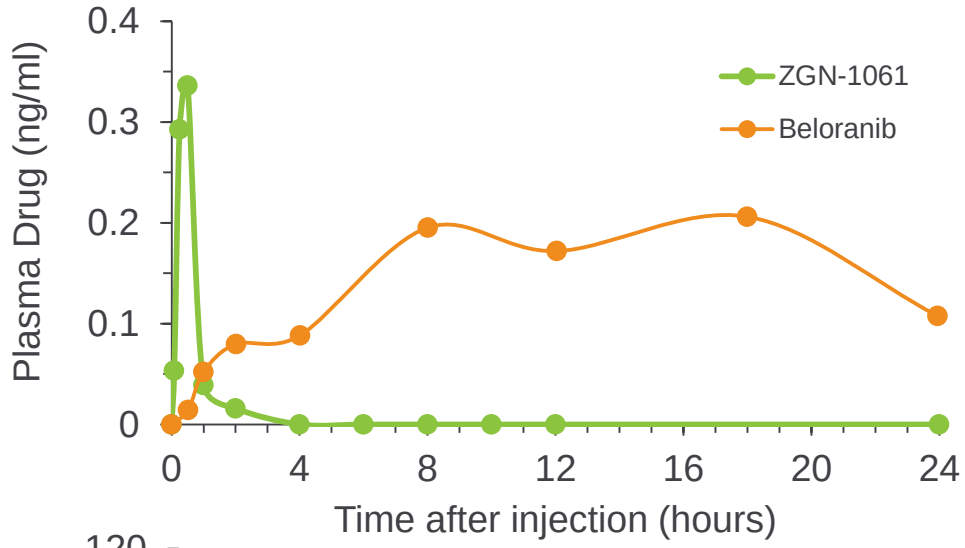


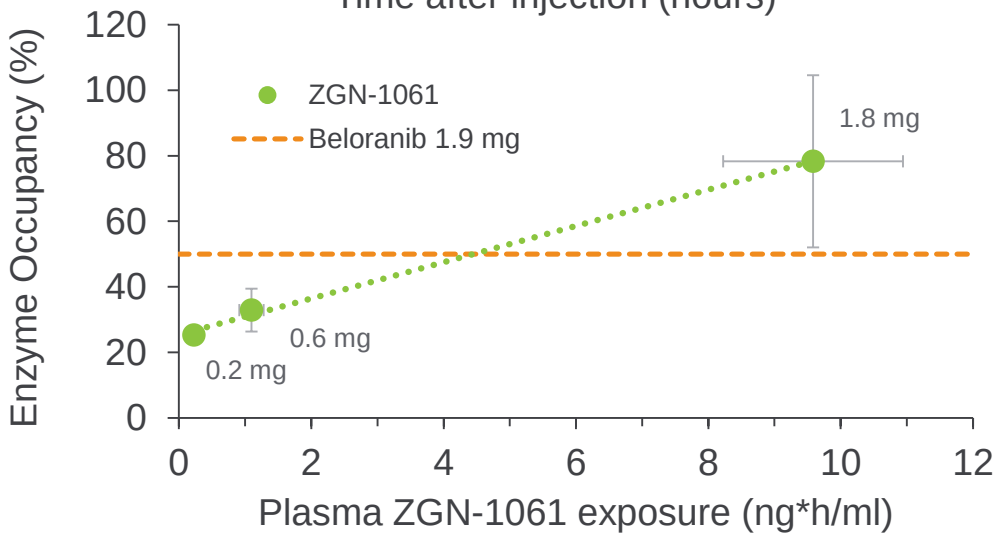
- C_{max} increased linearly with dose, with rapid absorption and a similarly rapid clearance over time
- T_{max} occurred within the first 30 minutes after dosing
- No plasma value of ZGN-1061 at the 8-hour or later timepoints reached the *in vitro* EC_{50} (0.12 ng/mL) value for required for inhibition of endothelial cell proliferation at 72h of incubation
- No ZGN-1061 was detected at the 12 hour or later time points

Values are mean ± SD

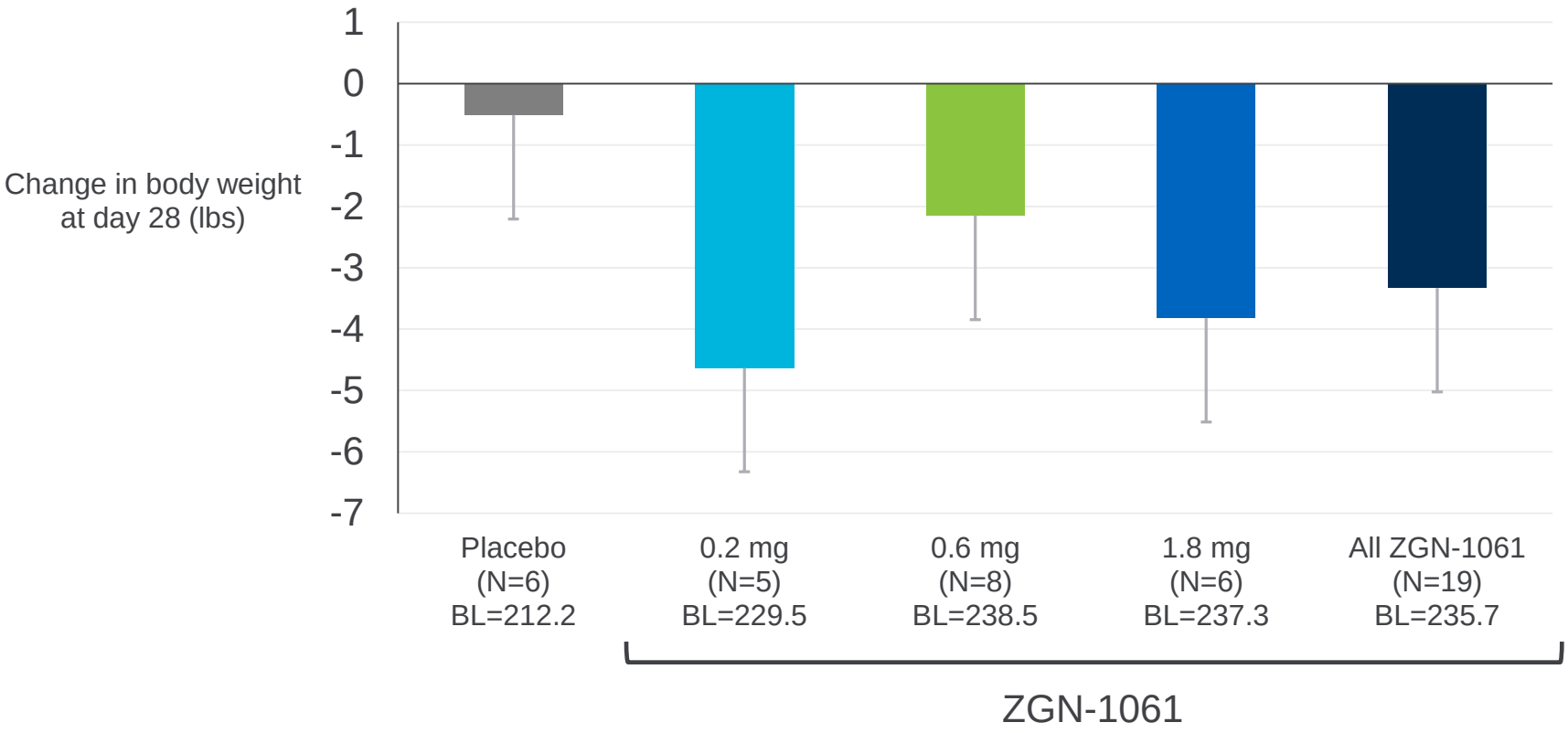
ZGN-1061 Exposure Profile Enables Rapid Target Engagement without Long-Term Exposure

- ZGN-1061 reaches effective concentrations rapidly, then is eliminated within hours
- Beloranib remains in circulation for over 24 hours, exceeding endothelial cell culture thresholds for prothrombotic actions
- ZGN-1061 exposure drives target engagement to a similar extent as beloranib at highly effective doses
- ZAF-1061-101 dose range reaches needed exposure leading to target engagement measured 24 hours after administration



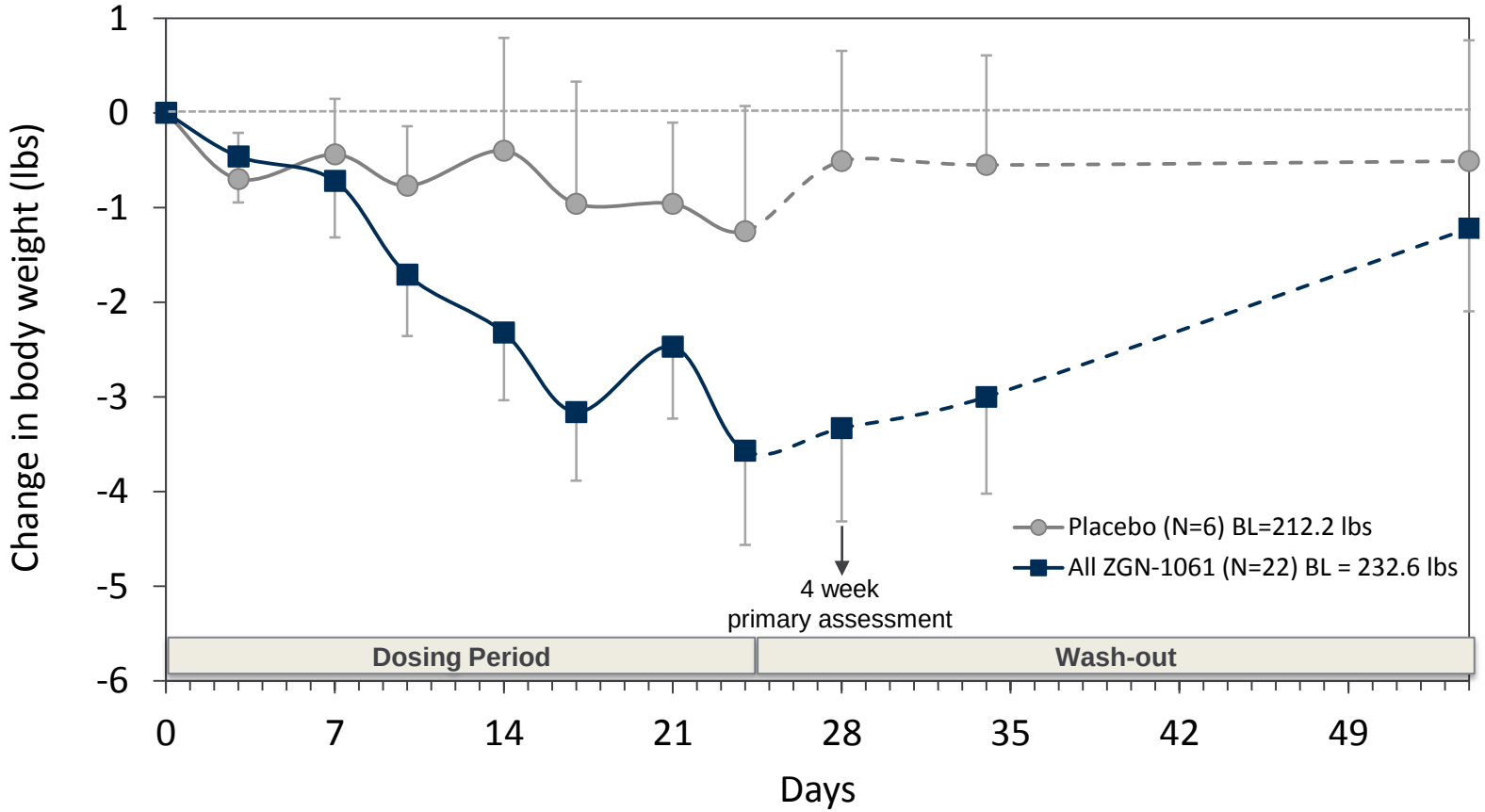


MAD Phase: Body Weight Change Shows Impact at All Dose Levels of ZGN-1061



- Weight reduction observed across all doses
- Majority of patients had weight changes in range of prior beloranib studies at active doses
- Additional titration of dose response including lower doses is needed – will be assessed in patients with type 2 diabetes in Phase 2

Body Weight Loss of Up to ~1 Pound per Week During Treatment Rebounds Post-Treatment, Supportive of Drug Effect



- Following discontinuation of treatment, ZGN-1061-treated patients on average experienced weight regain. This is supportive of a drug effect to lower body weight.
- Longer dosing is expected to drive continued weight loss as seen for beloranib

Trends for Improvement Across Multiple Metabolic Measures Supportive of Drug Activity

- Trends for improvements observed in:
  - Waist circumference
  - Food intake
  - Low density lipoprotein-cholesterol (LDL)
  - C-reactive protein (CRP)
  - Adiponectin
  - Leptin

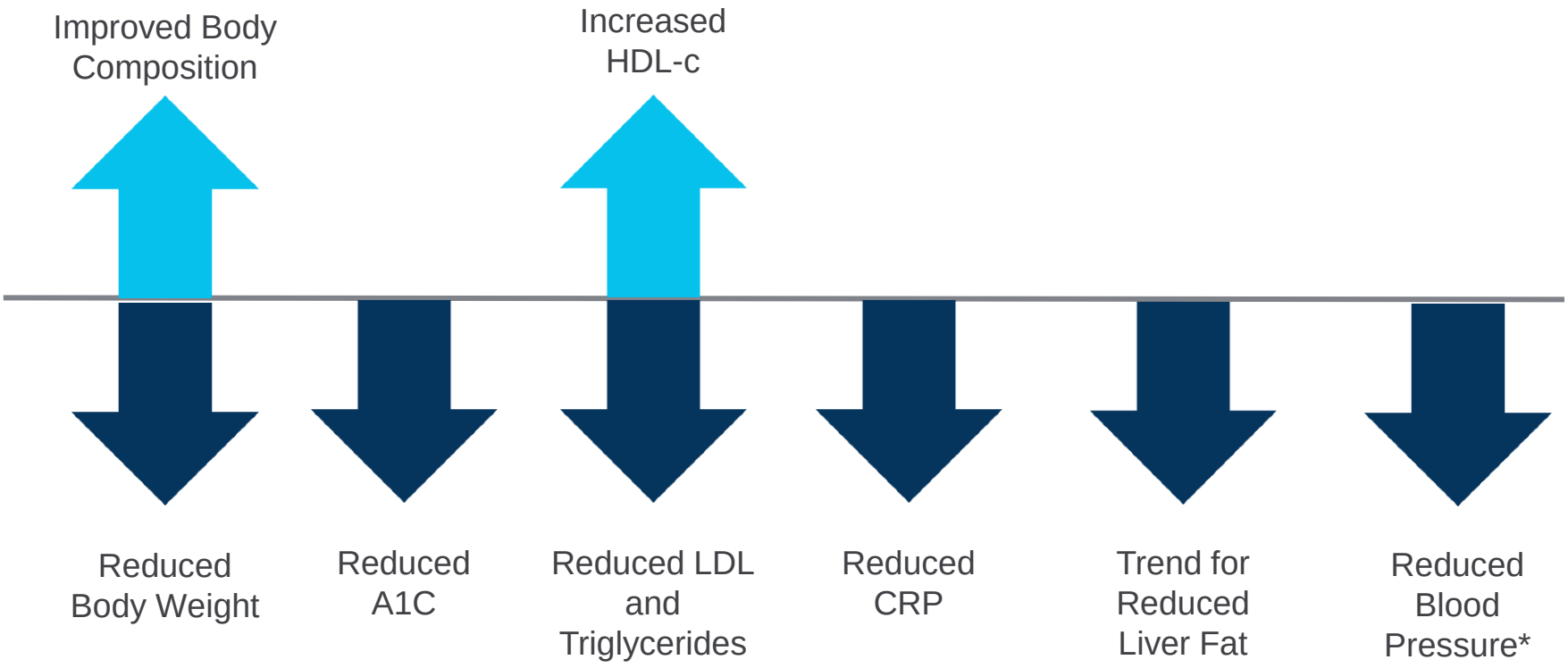
Key Findings in Top-Line Data

- Pharmacokinetic profile demonstrates rapid exposure and clearance
- Target engagement data supportive of effective exposure
- Efficacy data encouraging and supportive of drug effect
  - Up to approximately one pound/week average weight loss
  - Positive trends across multiple metabolic measures
- Overall safety/tolerability profile is clean, with no impact on sleep
- No prothrombotic effects observed with ZGN-1061
- Results support advancement into Phase 2 clinical trial

ZGN-1061: Next Steps

Tom Hughes, Ph.D., President and Chief Executive Officer

Vision for ZGN-1061: Addressing Broad Spectrum of Metabolic Dysregulation



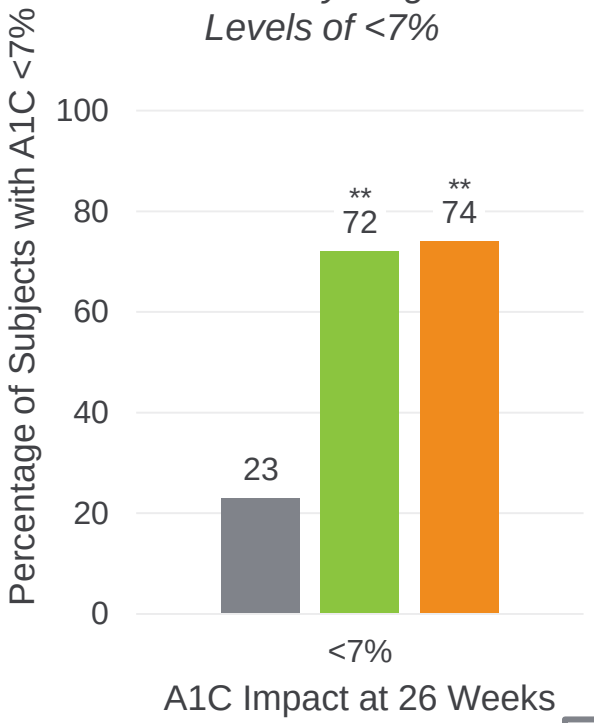
Benefits of MetAP2 inhibitor treatment point to potential ‘best in field’ efficacy impacting multiple difficult-to-treat comorbid conditions

* Results from ZAF-201 study using 24-hour blood pressure monitoring

MetAP2 Inhibition: Potential for Best-in-Field Impact on Glycemic Control and Weight Loss

Beloranib Phase 2b ZAF-203 Clinical Trial

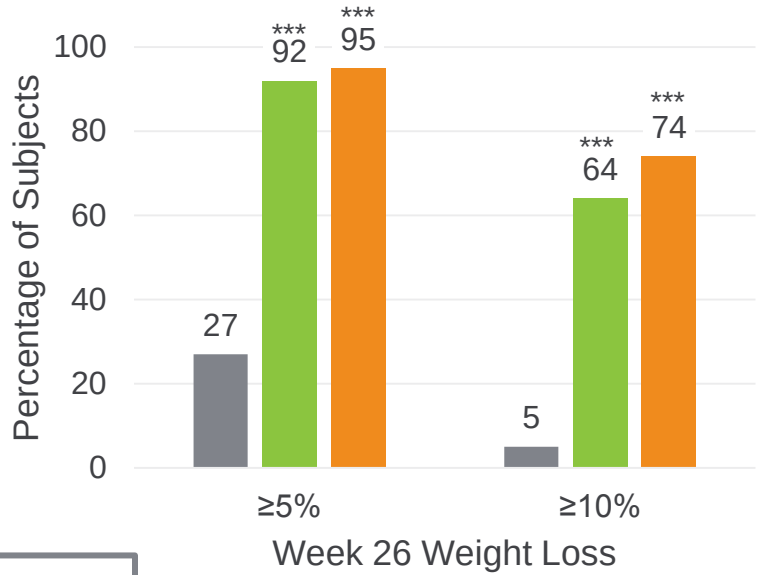
Majority of Treated Patients Achieved Key Target A1c Levels of <7%



A1C Impact at 26 Weeks

>90% of Treated Patients *experienced* **≥5%** weight loss

>60% of Treated Patients *experienced* **≥ 10%** weight loss



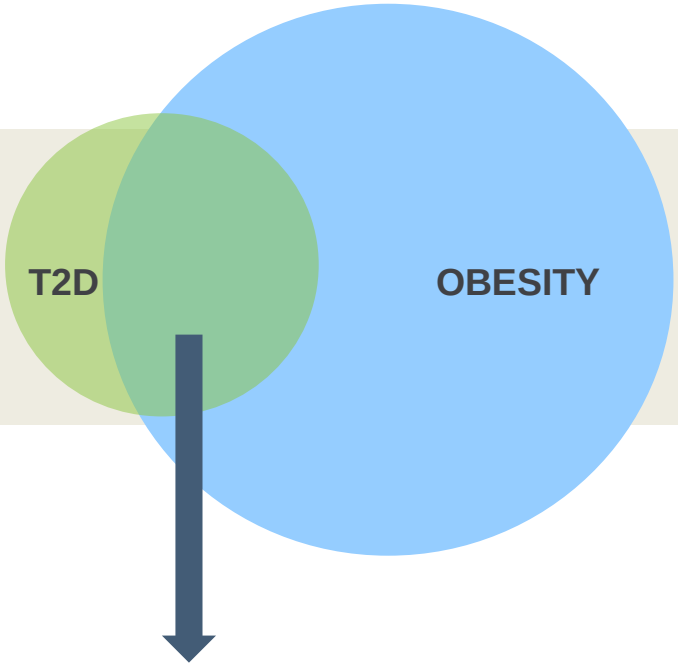
Week 26 Weight Loss

Placebo (N=22)
1.2 mg Beloranib (N=25)
1.8 mg Beloranib (N=19)

**p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

Unmet Medical Need in Type 2 Diabetes and Obesity

Type 2 Diabetes Market
- 25M patients
- $35B Rx market
- 80% of patients receive Rx
- More treatments needed due to progressive nature of disease



Obesity market
- 100M patients
- $500M Rx market
- 5% of patients receive Rx
- Few treatment options

Opportunity for ZGN-1061 to address patient segments of high unmet need

Patients who have failed numerous Rx options/procedures (bariatric surgery failures, patients who require insulin)

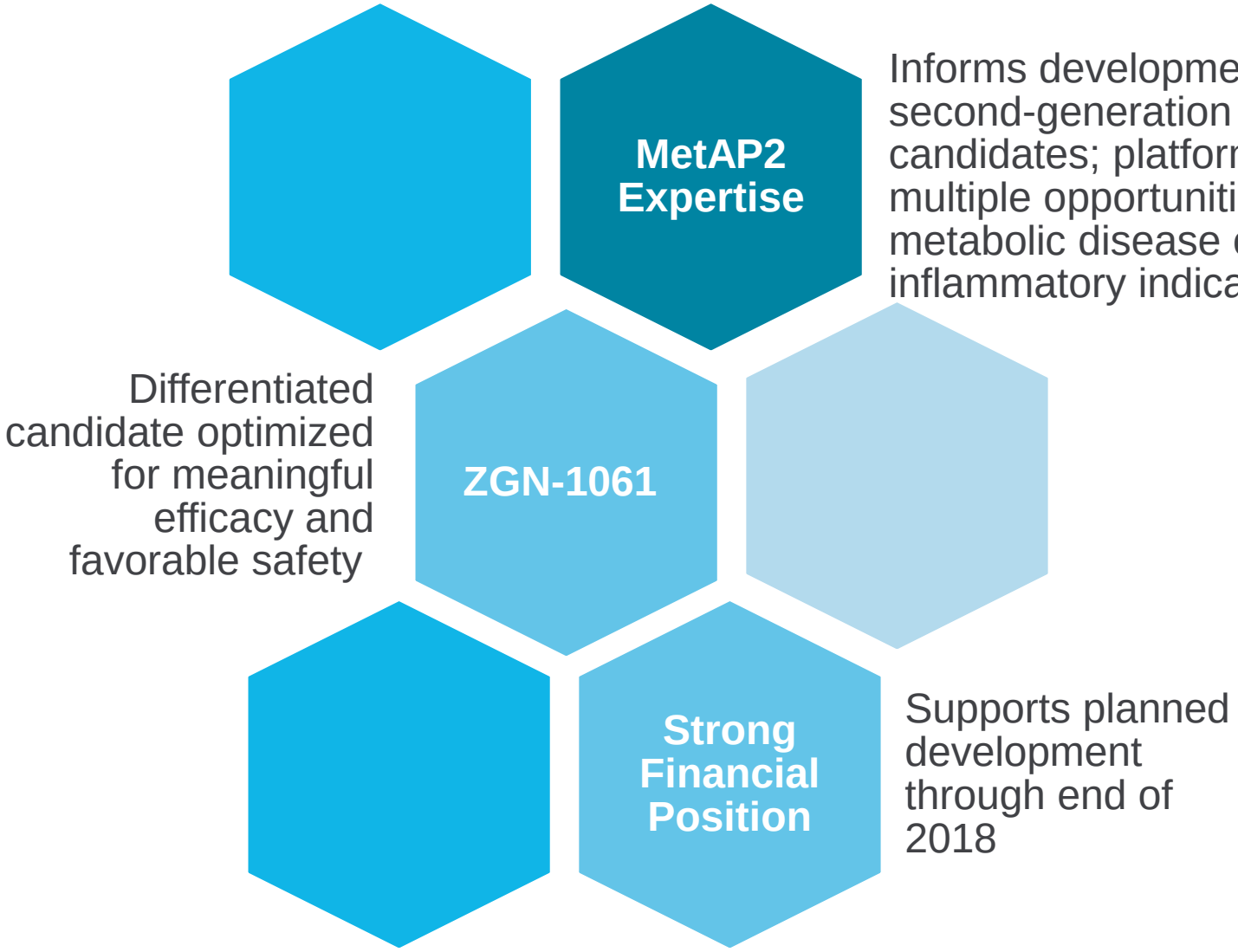
Patient segments defined by poor glycemic control, excess weight, inflammation, hyperlipidemia, and fatty liver

ZGN-1061: Next Steps

- Present complete ZAF-1061-101 results at a medical meeting
- Report additional non-clinical data supporting safety differentiation
- Begin Phase 2 clinical trial in patients with obesity and type 2 diabetes in Australia and New Zealand in 2H17
  - ~ 120 patients, 3-4 doses vs. placebo, 12 week treatment duration
- Refine manufacturing to support late stage development

Strong cash position to fund development through Phase 2;
Cash runway extends through 2018

Zafgen 2017: Leveraging Over a Decade of Experience in MetAP2 Inhibitor Development



Q&A