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Q1 2016 Financial Results & Business Update

May 10, 2016

Q1 2016 Financial Results

Prepared Remarks

- **Q1 Update**
  - Tom Hughes, Ph.D., Chief Executive Officer
- **Clinical Update**
  - Dennis Kim, M.D., Chief Medical Officer
- **Financial Results**
  - Patty Allen, Chief Financial Officer

Question and Answer Session

- **Also available for Q&A**
  - Patrick Loustau, President
  - Alicia Secor, Chief Commercial Officer

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 preclinical and clinical studies and our research and development programs, our ability to advance product candidates into, and successfully complete, clinical studies, the timing or likelihood of regulatory filings and approvals, and our expected cash, cash equivalents and marketable securities at year end 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 Annual Report on Form 10-K filed with the Securities and Exchange Commission, as updated by our future filings with the Securities and Exchange Commission, including without limitation, Zafgen’s ability to obtain a release of the full clinical hold placed on the beloranib IND. 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.

Q1 Update

Tom Hughes, Ph.D.
Chief Executive Officer

Recent Clinical Developments

- bestPWS Phase 3 ZAF-311 Data in PWS
  - Top-line results in January 2016; full data presentation at ENDO 2016
  - Beloranib achieved co-primary endpoints, with statistically significant and clinically meaningful improvements in hyperphagia-related behaviors and body weight
  - Statistically significant reduction in total body mass and fat mass
  - Improvements in lipids and markers of cardiometabolic risk

- Phase 2b ZAF-203 Data in Severe Obesity Complicated by Type 2 Diabetes
  - Top-line results in February 2016
  - Achieved primary and key secondary endpoints
  - Statistically significant and clinically meaningful improvements in body weight and glycemic control

Addressing the Beloranib Clinical Hold

✓	**bestPWS ZAF-311 Data**
✓	**ZAF-203 Data in Severe Obesity Complicated by Type 2 Diabetes**
✓	**Clinical and Non-clinical Risk Assessment**
✓	**Risk Mitigation Strategy**

Demonstrate Efficacy: Impact of Treatment, Clinical Relevance and Robustness of Effects

Demonstrate Benefit/Risk from Full Program; Integrated AE Profile

Risk Mitigation Proposal to Screen / Monitor / Mitigate Thrombotic Risk

Next steps: Advancing toward discussions with the FDA

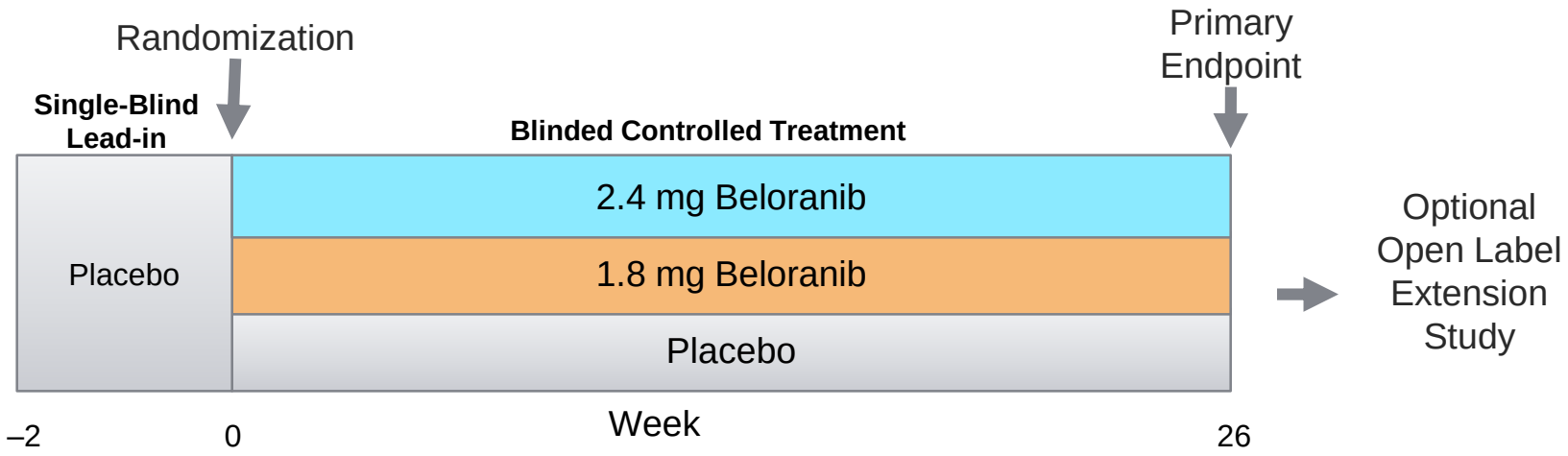
Clinical Update

Dennis Kim, M.D.
Chief Medical Officer

Positive Efficacy Results for bestPWS and ZAF-203

bestPWS ZAF-311 Phase 3 Data	Phase 2b ZAF-203 Data
Prader-Willi Syndrome	Severe Obesity with Type 2 Diabetes
• Achieved both co-primary endpoints, key secondary endpoints • Statistically significant and clinically meaningful reduction in hyperphagia-related behaviors and body weight • Improvements in body fat composition, lipids and cardiometabolic risk factors	• Achieved primary and key secondary endpoints • Statistically significant and clinically meaningful improvements in body weight and glycemic control • Improvements in body fat composition, lipids and cardiometabolic risk factors

bestPWS ZAF-311 Pivotal Phase 3 Study Design

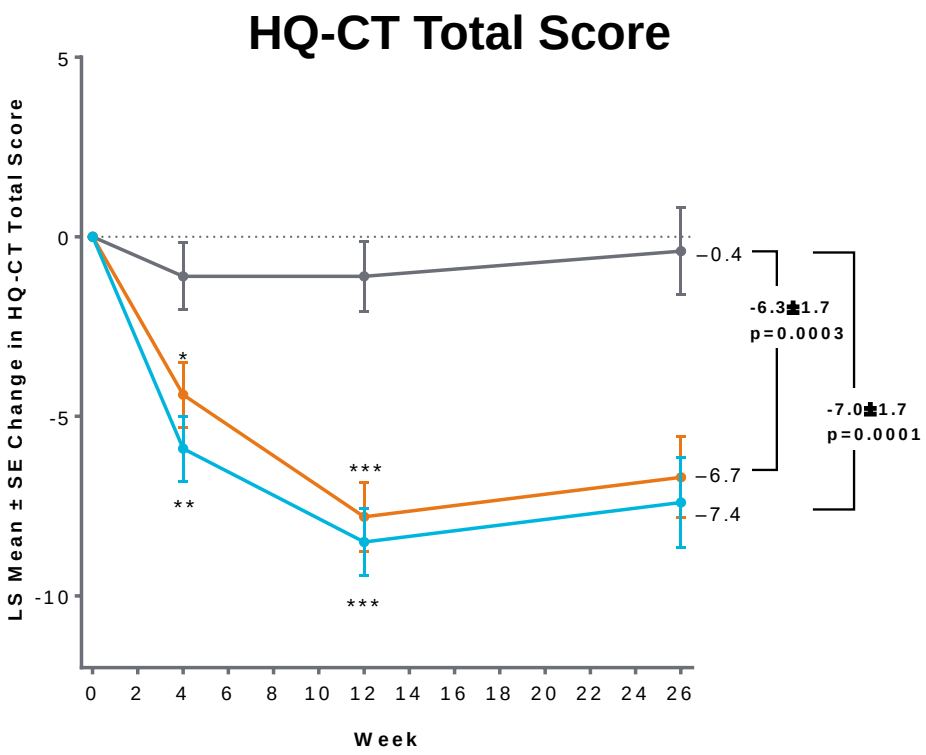


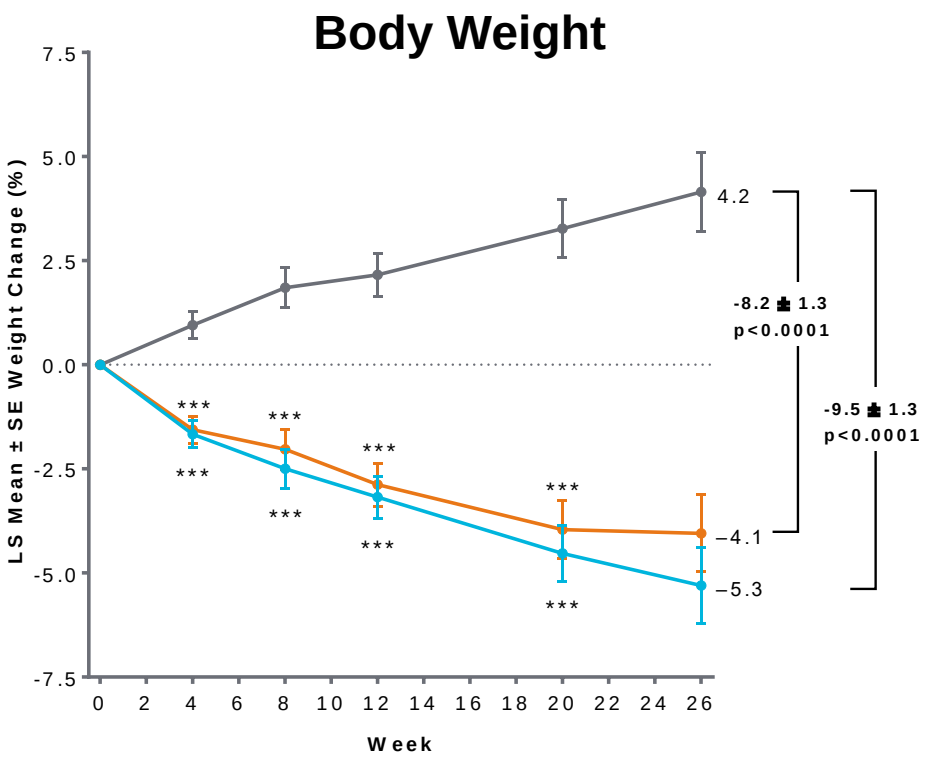
- Co-primary endpoints: improvement in hyperphagia-related behaviors and body weight
- Secondary endpoints: body fat mass, LDL-c, HDL-c, C-reactive protein
- 107 patients randomized
  - Baseline characteristics well-balanced among the three treatment groups
  - Study population representative of general PWS population

Placebo includes placebo low-volume and placebo high-volume. Subjects randomized to 2.4 mg beloranib and all subjects in the OLE received 1.8 mg beloranib for the first 4 weeks of treatment. All doses were administered twice-weekly by subcutaneous injection.

bestPWS Study Achieves Co-Primary Efficacy Endpoints ITT Population (N=107)

- Statistically significant reduction in hyperphagia and body weight at both doses





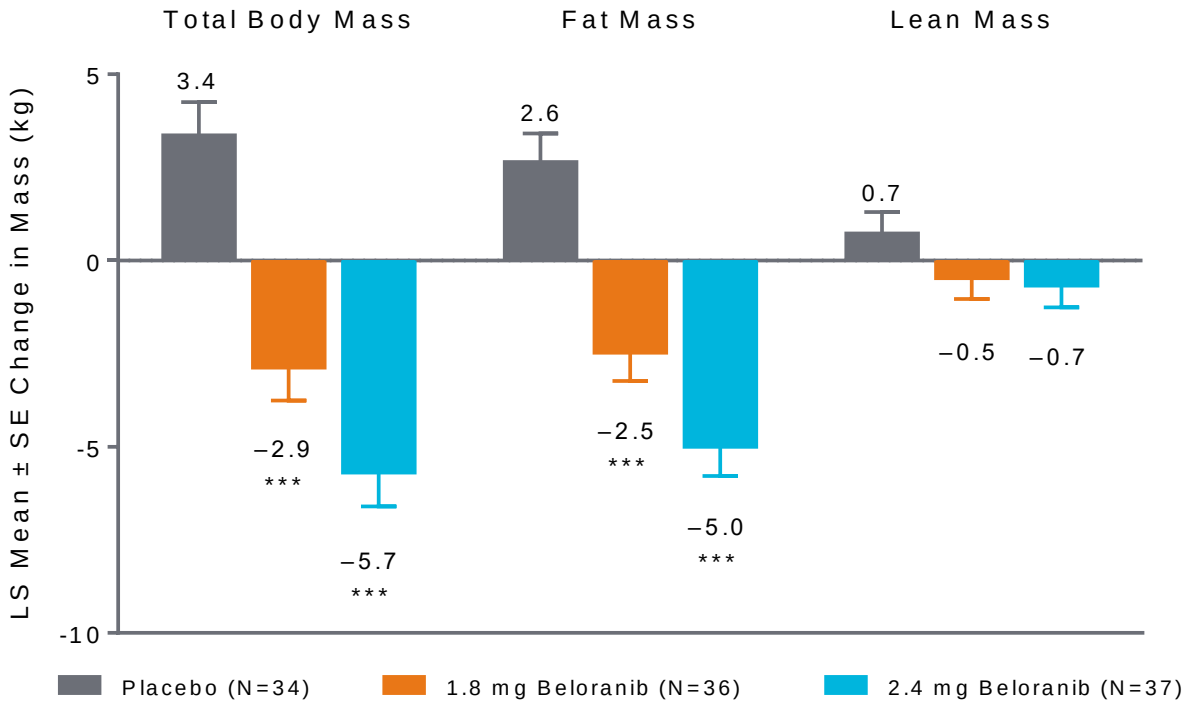
Placebo (N=34); BL Wt=100.9 kg; BL HQ-CT=15.0

1.8 mg Beloranib (N=36); BL Wt = 97.5 kg; BL HQ-CT=17.4

2.4 mg Beloranib (N=37); BL Wt=105.7 kg; BL HQ-CT=18.3

*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo.
Analysis is implemented via a mixed model repeated measures (MMRM) model.

bestPWS: Beloranib Produced Statistically Significant Improvements in Body Composition



Baseline

	Total Mass (kg)	Fat Mass (kg)	Lean Mass (kg)
Placebo	96.3	51.5	43.2
1.8 mg beloranib	91.5	47.6	42.2
2.4 mg beloranib	98.5	53.2	43.6

*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

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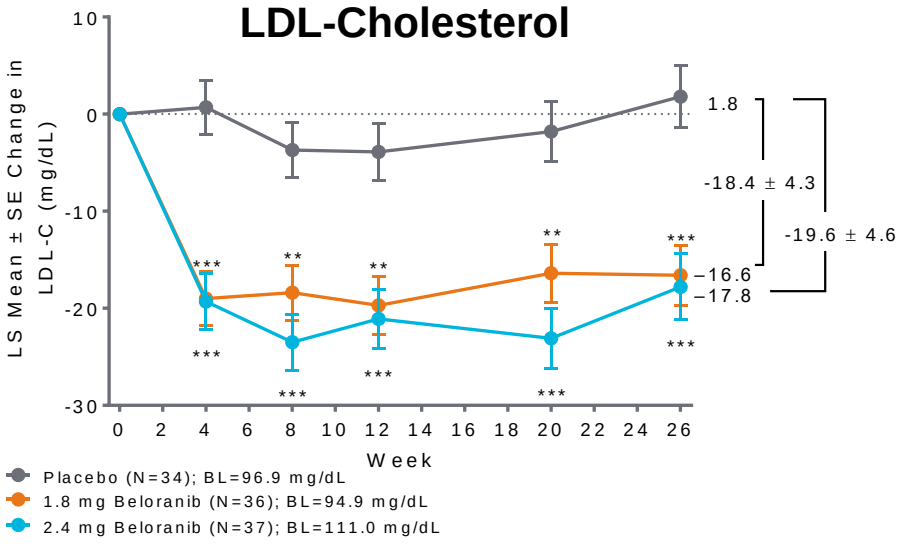
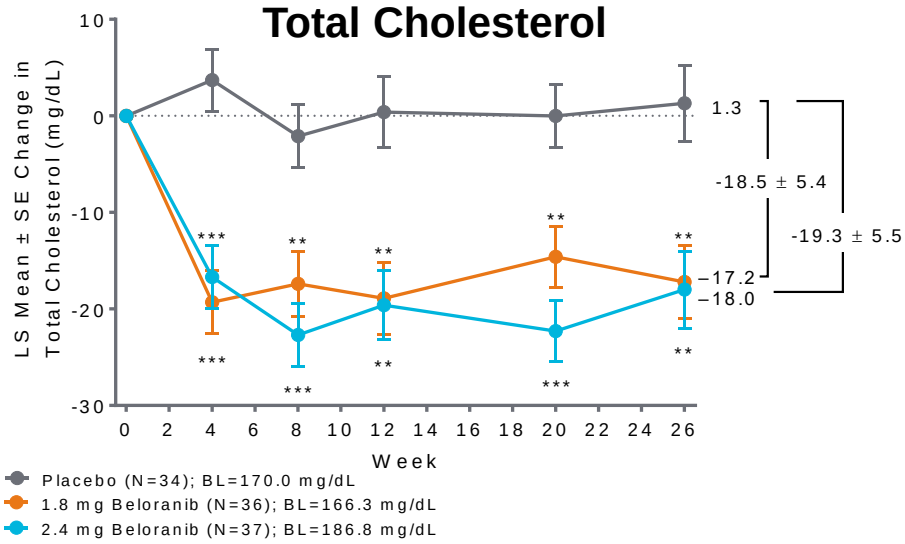
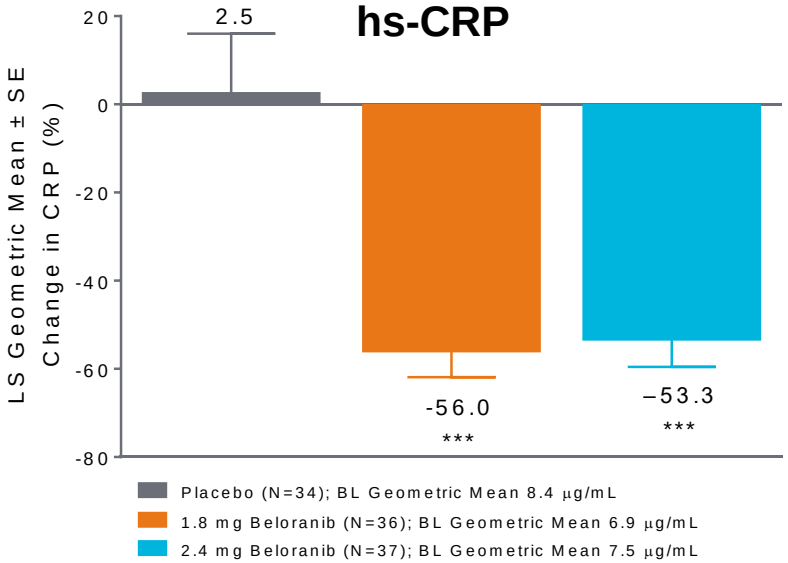
bestPWS: Beloranib Associated with Improvements in Markers of Cardiometabolic Risk







*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

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Overview of Adverse Events (AE) and Serious Adverse Events (SAE) Related to Thrombosis

Beloranib IND was placed on a full clinical hold by the FDA on December 2, 2015. Across nine clinical trials evaluating >500 patients, 11 patients had thrombotic events, of which five patients had SAEs. Thrombotic events to date seen only in patients randomized to beloranib.

Study	Dose	Event	Causality per Investigator	Additional Info
ZAF-201 (completed)	1.2mg	SAE of pulmonary embolism (PE); thrombophlebitis	Not related	Factor V Leiden mutation
	2.4mg	SAE of PE; Deep vein thrombosis (DVT)	Not related	Gout attack and extended immobilization
	2.4mg	Moderate AE of thrombophlebitis superficial	Not related	Varicose veins; Implanted contraceptive
	2.4mg	Mild AE of thrombophlebitis superficial	Not related	Implanted contraceptive
ZAF-203 (completed)	1.2mg	SAE of PE	Not related	Implanted contraceptive; heart failure; systemic pulmonary inflammatory disease
	1.8mg	Moderate AE of DVT	Related	Discovered during VTE screening, 4 weeks after last dose of study drug. Two 8-hour flights occurring 3-4 weeks prior to VTE screening.
	1.2mg	Moderate AE of thrombophlebitis superficial	Related	Discovered during VTE screening, 19 weeks after last dose of study drug. Ongoing medical history of bilateral superficial venous insufficiency
ZAF-311 (completed)	1.8mg	Moderate AE of thrombophlebitis superficial; DVT	Possibly related	Extended (6 hour) car ride
	2.4mg	Moderate AE of DVT	Possibly related	Androgel 1% transdermal patch
	1.8mg	SAE of PE; death; DVT confirmed upon autopsy	Possibly related	BMI 55 with multiple co-morbidities
	2.4mg	SAE of PE; death; thrombophlebitis superficial	Probably related	Ongoing thrombophlebitis superficial (prior history); treated with ASA

1Q16 Financial Results

Patty Allen
Chief Financial Officer

1Q 2016 Selected Financial Summary

Balance Sheets	As of March 31, 2016	As of March 31, 2015	As of December 31, 2015
Cash, Cash Equivalents and Marketable Securities	$ 166.2M	$ 234.2M	$ 185.1M
Total Assets	$170.0M	$ 236.7M	$ 189.1M

Statements of Operations	Quarter Ended March 31, 2016	Quarter Ended March 31, 2015	Quarter Ended December 31, 2015
Research & Development Expenses	$ 12.5M	$ 10.2M	$ 17.7M
General & Administrative Expenses	$ 5.4M	$ 3.0M	$ 5.5M
Net Loss	($ 17.7)M	($ 13.5)M	($ 23.2)M
Net Loss per Share	($0.65)	($0.53)	($0.85)

- Expect to end 2016 with greater than $100 million in cash
  - Strong position to drive our programs forward
  - Plan to provide more specific guidance following potential resolution of full clinical hold

Closing Remarks

Tom Hughes, Ph.D.
Chief Executive Officer

Q&A

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Thank You

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