ZAF-203: Beloranib in Obese Subjects with Type 2 Diabetes

February 18, 2016

Disclaimers

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Introduction

Tom Hughes, Ph.D.
Chief Executive Officer

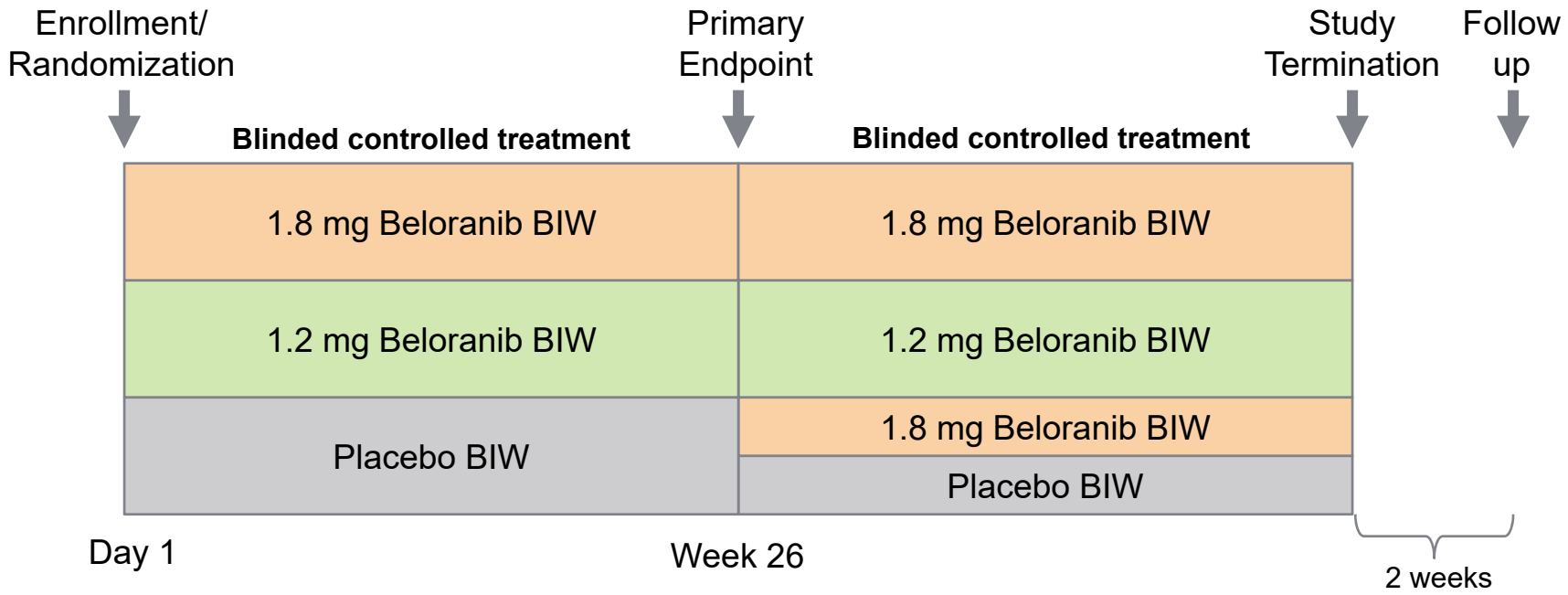
ZAF-203 Study Results

Dennis Kim, M.D.

Chief Medical Officer

ZAF-203: Clinical Study Design

- Phase 2, randomized, double-blind, parallel comparison study of 2 doses of beloranib vs. placebo for 26 weeks with an additional 26-week blinded controlled treatment period



Placebo includes placebo low-volume and placebo high-volume. Subjects randomized to 1.8 mg Beloranib received 1.2 mg Beloranib for the first 4 weeks of each blinded treatment period. Follow up assessments were conducted at 4 days and 2 weeks after study termination.

ZAF-203: Study Endpoints

- Primary Efficacy Endpoint
  - Weight change (percent and absolute) at Week 26
- Secondary Endpoints
  - Proportion of subjects with weight loss ≥5%, ≥10%, ≥15%, and ≥20% at Week 26
  - Change in fasting glycemic parameters and cardiometabolic parameters at Week 26
  - Change in Patient-Reported Outcome scores at Week 26
  - Pharmacokinetics of beloranib
  - Change in glycemic parameters during mixed meal tolerance test (MMTT)

Patient Disposition

n (%)	Placebo (N=51)	1.2 mg Beloranib (N=52)	1.8 mg Beloranib (N=50)	Placebo/1.8 mg Beloranib (N=10)	Overall (N=153)
Safety Population	51 (100%)	52 (100%)	49 (98%)	n/a	152 (99.3%)
Intent-to-Treat (ITT) Population	51 (100%)	52 (100%)	49 (98%)	n/a	152 (99.3%)
Completed 26 Week Randomized Treatment Period	24 (47.1%)	26 (50.0%)	20 (40.0%)	n/a	70 (45.8%)
Treatment Discontinuation During 26 Week Period	27 (52.9%)	26 (50.0%)	30 (60.0%)	n/a	83 (54.2%)
Adverse event	2 (3.9%)	4 (7.7%)	5 (10.0%)	n/a	11 (7.2%)
Discontinued due to Clinical Hold	24 (47.1%)	21 (40.4%)	20 (40%)	n/a	65 (42.5%)
Per Protocol (PP) Population	22 (43.1%)	25 (48.1%)	19 (38.0%)	n/a	66 (43.1)
Treatment Discontinuation After 26 Week Period					
Adverse event	0	1 (1.9%)	0	0	1 (0.7%)
Discontinued due to Clinical Hold	24 (47.1%)	25 (48.1%)	20 (40.0%)	10 (100.0%)	69 (45.1%)

Placebo/1.8 mg group contains subjects assigned to Placebo at Day 1 and 1.8 mg at Week 26. n/a = not applicable.

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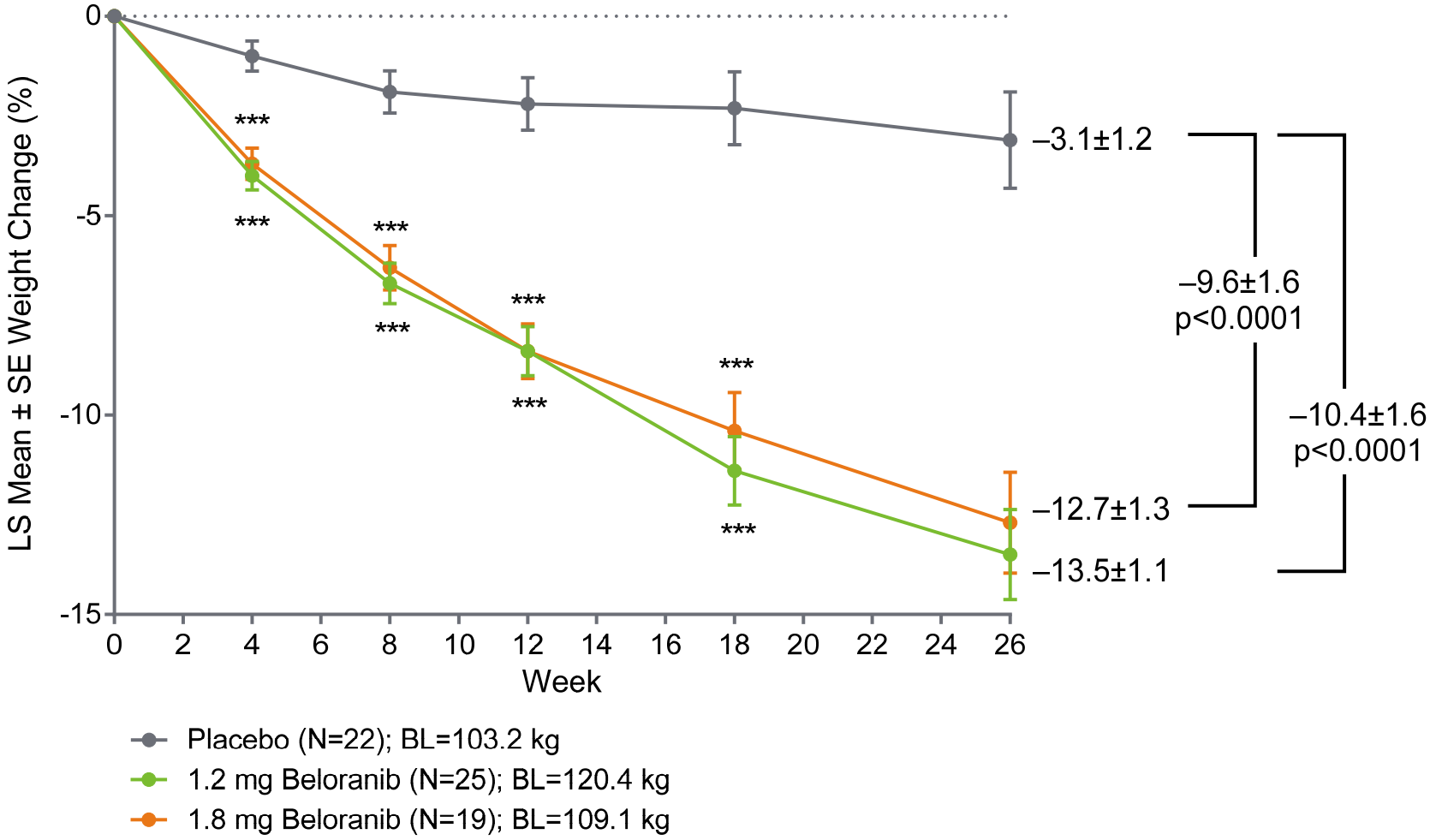
Baseline Demographics and Characteristics Per Protocol Population (N=66)

Adverse Event	Placebo N=22	1.2 mg Beloranib N=25	1.8 mg Beloranib N=19
Age, y	55.7 ± 4.9	54.0 ± 7.1	54.9 ± 7.3
Sex (% Male)	45.5%	52.0%	52.6%
Race (% White/Asian/Other)	91/5/5%	92/0/8%	90/0/10%
Weight, kg	103.2 ± 16.4	120.4 ± 22.8	109.1 ± 18.7
BMI, kg/m^2	37.8 ± 4.9	41.6 ± 7.0	36.9 ± 5.6
HbA1c, %	8.1 ± 1.0	8.5 ± 1.1	8.2 ± 1.0
Fasting Plasma Glucose, mg/dL	183.4 ± 44.8	199.9 ± 49.8	199.2 ± 48.0

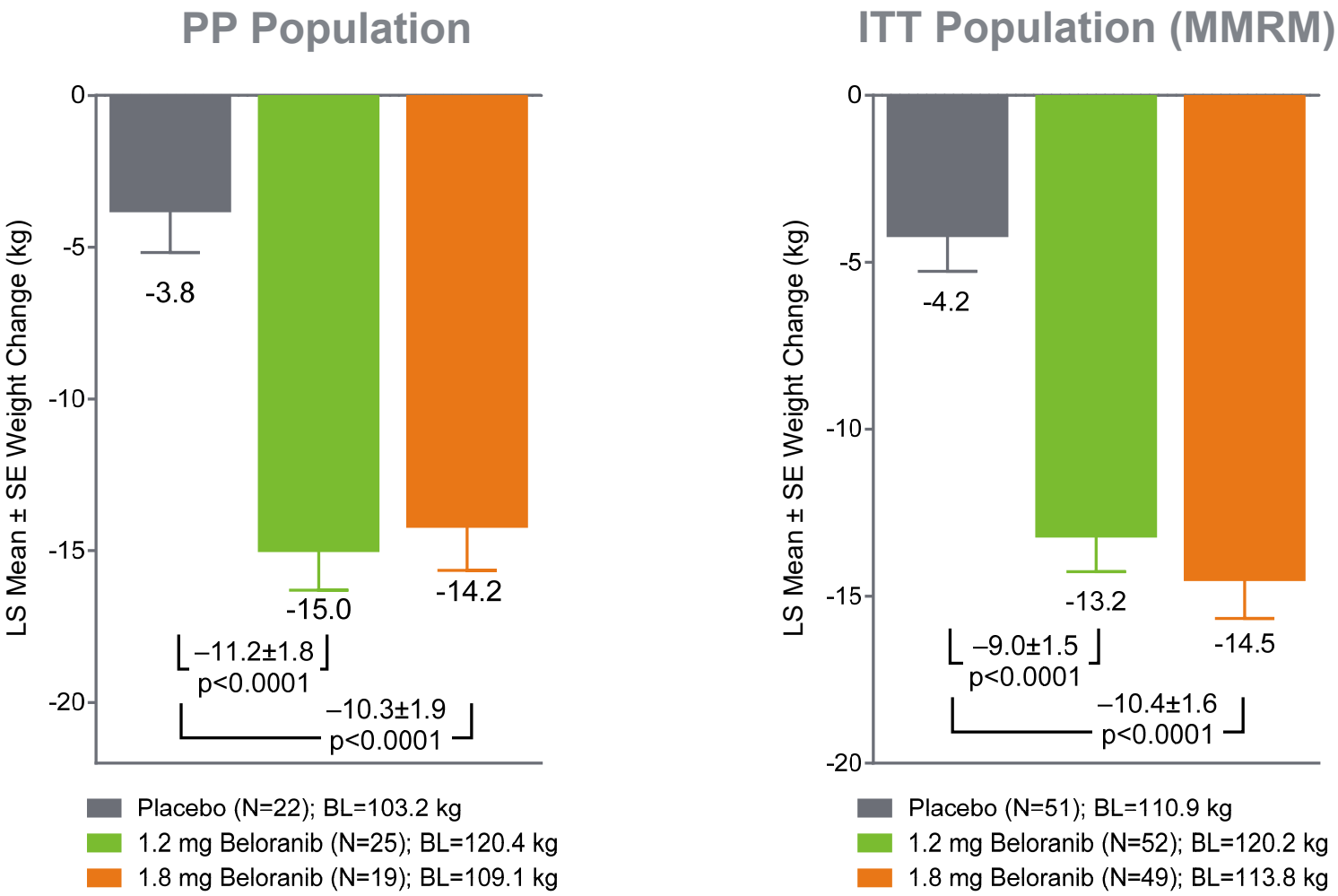
Data are Mean ± SD or % for the Per Protocol Population.

Beloranib Resulted in Statistically Significant Weight Loss vs. Placebo (PP Population)



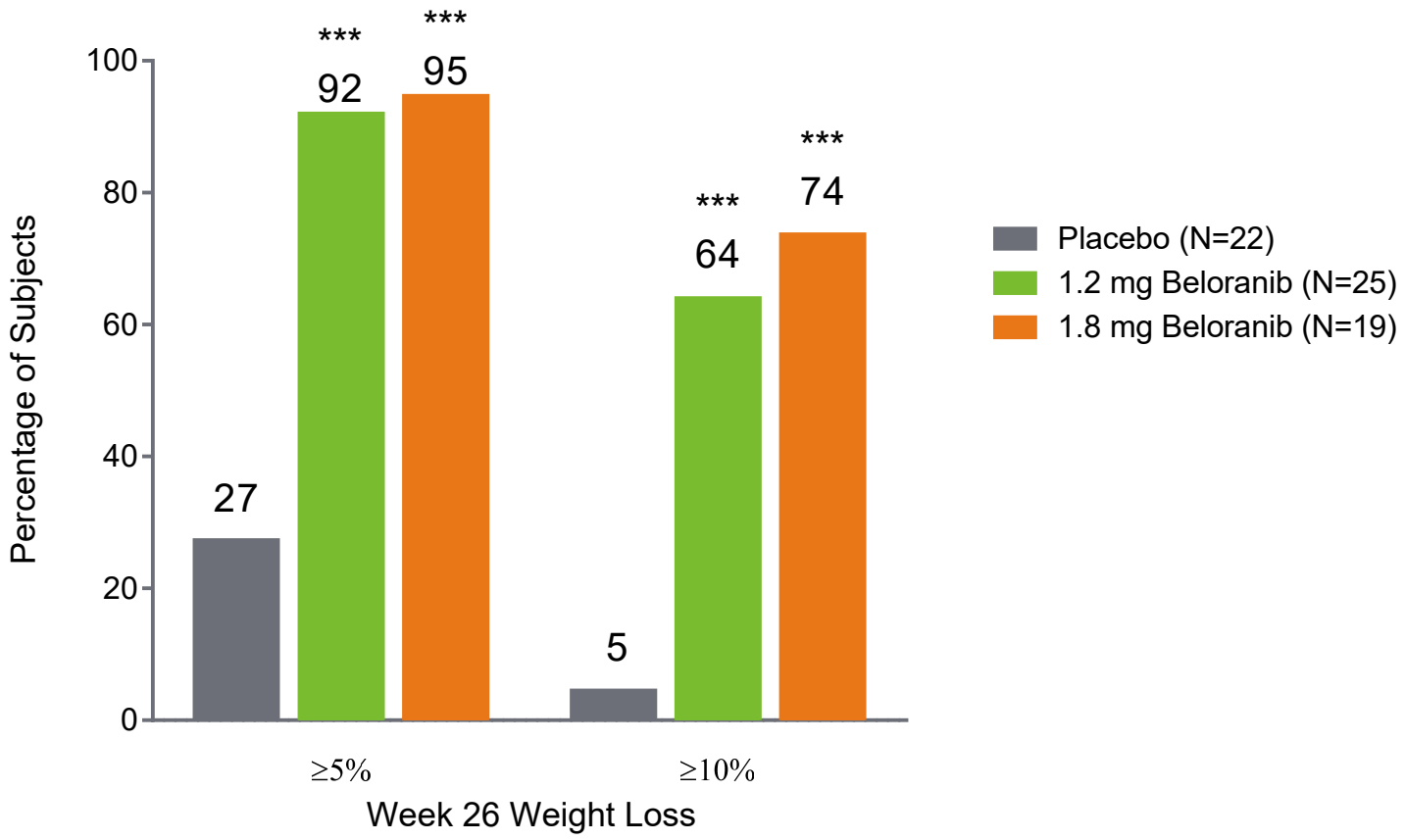
*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo.

Absolute Weight Change at Week 26 Consistent Across PP and ITT Populations



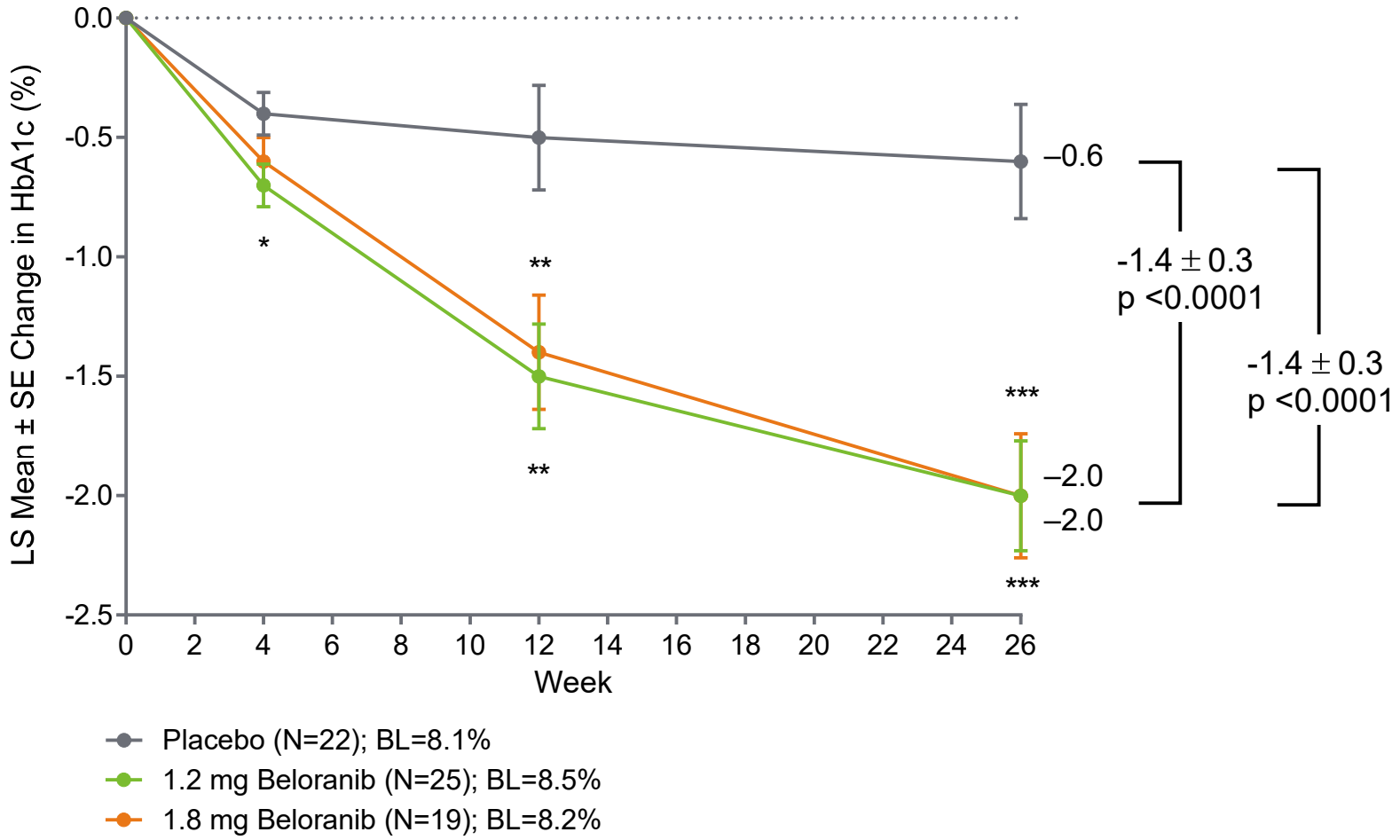
Over 90% of Patients Treated with Beloranib Achieved Target Weight Loss ≥5% (PP Population)

Percentage of Subjects with Weight Loss ≥5% and ≥ 10% at Week 26



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

Beloranib Treatment Improved Glycemic Control Over 26 Weeks (PP Population)



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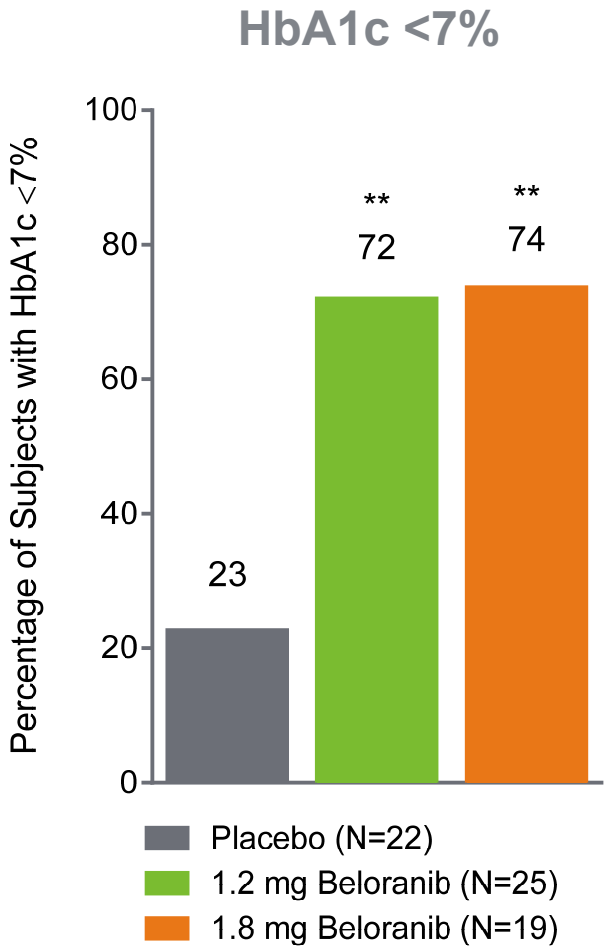
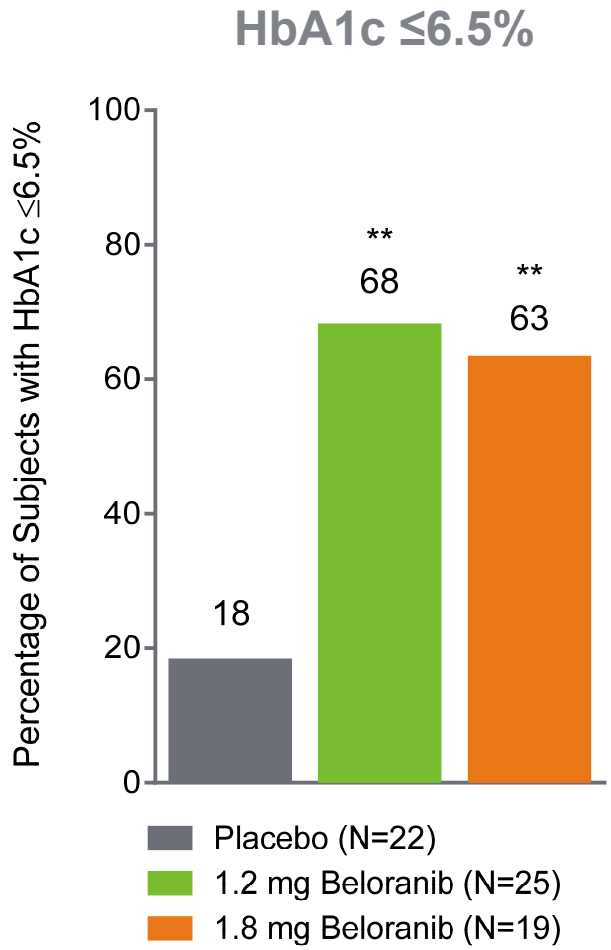
Majority of Subjects Treated with Beloranib Achieved Key Target Levels for HbA1c at Week 26 (PP Population)





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

Summary of Treatment-Emergent Adverse Events Safety Population (N=152)

n (%)	Placebo N=51	1.2 mg Beloranib N=52	1.8 mg Beloranib N=49	Placebo/1.8 mg Beloranib N=10
Any Treatment Emergent Adverse Events (TEAE)	43 (84.3%)	48 (92.3%)	41 (83.7%)	9 (90.0%)
Serious TEAE (SAE)	2 (3.9%)	5 (9.6%)	1 (2.0%)	0
TEAE leading to withdrawal of study drug	2 (3.9%)	5 (9.6%)	5 (10.2%)	0
TEAE events by maximum severity				
Mild	18 (35.3%)	16 (30.8%)	12 (24.5%)	4 (40.0%)
Moderate	18 (35.3%)	23 (44.2%)	23 (46.9%)	5 (50.0%)
Severe	7 (13.7%)	9 (17.3%)	6 (12.2%)	0

Data are n (%) of subjects and number of adverse events for the Safety Population, which includes all subjects who received at least 1 dose of randomized study drug.

Frequent Treatment Emergent Adverse Events Safety Population (N=152)

Adverse Event	Placebo N=51	1.2 mg Beloranib N=52	1.8 mg Beloranib N=49	Placebo/1.8 mg Beloranib N=10
Any TEAE	43 (84.3%) 235	48 (92.3%) 268	41 (83.7%) 229	9 (90.0%) 21
Upper respiratory tract infection	10 (19.6%) 12	15 (28.8%) 19	7 (14.3%) 8	1 (10.0%) 1
Diarrhoea	8 (15.7%) 8	10 (19.2%) 12	9 (18.4%) 12	2 (20.0%)2
Injection site bruising	7 (13.7%) 11	10 (19.2%) 10	7 (14.3%) 10	0
Abnormal dreams	1 (2.0%) 1	8 (15.4%) 8	4 (8.2%) 4	1 (10.0%)
Sleep disorder	1 (2.0%) 1	5 (9.6%) 5	7 (14.3%) 7	0
Lower respiratory tract infection	2 (3.9%) 2	7 (13.5%) 7	3 (6.1%) 3	0
Nausea	11 (21.6%) 13	5 (9.6%) 6	4 (8.2%) 5	1 (10.0%) 1
Headache	9 (17.6%) 14	7 (13.5%) 9	2 (4.1%) 2	0
Cough	2 (3.9%) 2	3 (5.8%) 3	5 (10.2%) 5	0
Injection site erythema	1 (2.0%) 3	2 (3.8%) 2	6 (12.2%) 7	0

Data are number of patients, (%), and number of events for the Safety Population, which includes all subjects who received at least 1 dose of randomized study drug. Placebo/1.8 mg beloranib includes any events that began after Week 26 (on 1.8 mg beloranib) and are the same subjects represented within the placebo column. Terms were included if ≥10% incidence in the placebo, 1.2 mg beloranib or 1.8 mg beloranib treatment arms.

All Serious Adverse Events Safety Population (N=152)

N (%) events	Placebo N=51	1.2 mg Beloranib N=52	1.8 mg Beloranib N=49	Placebo/1.8 mg Beloranib N=10
Any SAE	2 (3.9%) 2	5 (9.6%) 6	1 (2.0%) 1	0
Abdominal pain lower	1 (2.0%) 1	0	0	0
Acute myocardial infarction	0	1 (1.9%) 1	0	0
Atrial fibrillation	0	1 (1.9%) 1	0	0
B-cell lymphoma	0	1 (1.9%) 1	0	0
Exostosis	0	0	1 (2.0%) 1	0
Musculoskeletal chest pain	0	1 (1.9%) 1	0	0
Nephrolithiasis	1 (2.0%) 1	0	0	0
Psychotic disorder	0	1 (1.9%) 1	0	0
Pulmonary embolism	0	1 (1.9%) 1	0	0

Data are number of patients, (%), and number of events for the Safety Population, which includes all subjects who received at least 1 dose of randomized study drug.

TEAE Leading to Study Discontinuation Safety Population (N=152)

Adverse Event	Placebo N=51	1.2 mg Beloranib N=52	1.8 mg Beloranib N=49	Placebo/1.8 mg Beloranib N=10	All Beloranib N=111
Subjects Withdrawing Due to TEAE	2 (3.9%)	5 (9.6%)	5 (10.2%)	0 (0.0%)	10 (9.0%)
Alopecia	0 (0.0%)	1 (1.9%)	1 (2.0%)	0 (0.0%)	2 (1.8%)
Insomnia	0 (0.0%)	2 (3.8%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
Abnormal dreams	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (0.9%)
Depression	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (0.9%)
Nausea	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (0.9%)
Pulmonary embolism	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Sleep disorder	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (0.9%)
Social avoidant behavior	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Dizziness	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hot flush	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Muscle spasms	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin tightness	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data are number (%) of adverse events for the Safety Population, which includes all subjects who received at least 1 dose of randomized study drug. Placebo/1.8 mg beloranib includes any events that began after Week 26 (on 1.8 mg beloranib) and are the same subjects represented within the placebo column. Some subjects reported more than one adverse event as their reason for withdrawal.

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. Six AE and five SAE related to thrombosis observed across nine clinical trials evaluating >500 patients. 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	Possibly related	BMI 55 with multiple co-morbidities
	2.4mg	SAE of PE; death	Probably related	Ongoing thrombophlebitis superficial (prior history); treated with ASA

ZAF-203 Conclusions

Beloranib resulted in statistically significant and clinically meaningful reductions in body weight and HbA1c in obese patients with type 2 diabetes:

- Demonstrated ~13% reduction in body weight vs. 3% reduction in placebo
- >90% of per protocol subjects receiving beloranib achieved ≥ 5% weight loss, with more than 60% achieving ≥ 10% weight loss
- On average, subjects achieved an HbA1c of 6.3% from an initial baseline of 8.3%
- Approximately 75% of patients receiving beloranib were at or below target HbA1c goal of 7% after 6 months

Safety and tolerability consistent with prior clinical trials in conventional obesity; 3 VTEs were observed in beloranib treatment groups

Next Steps with Beloranib

Tom Hughes, Ph.D.
Chief Executive Officer

Establishing the Benefit / Risk Relationship and Mitigation Plan for Beloranib in PWS

Items to be Submitted to FDA in Effort to Resolve Hold

✓	**bestPWS ZAF-311 Data**
✓	**ZAF-203 Data**
Developing	**Clinical and Non-clinical Risk Assessment**
Developing	**Risk Mitigation Strategy**

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

Demonstrate Risk / Benefit from Full Program; Integrated AE Profile

Risk Mitigation Proposal to Screen / Monitor / Mitigate Thrombotic Risk

Q&A

Management