

# First-in-Human Study of an Oral Formulation of the GLP-1/GIP Co-Agonist VK2735 in Healthy Adults

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## Background

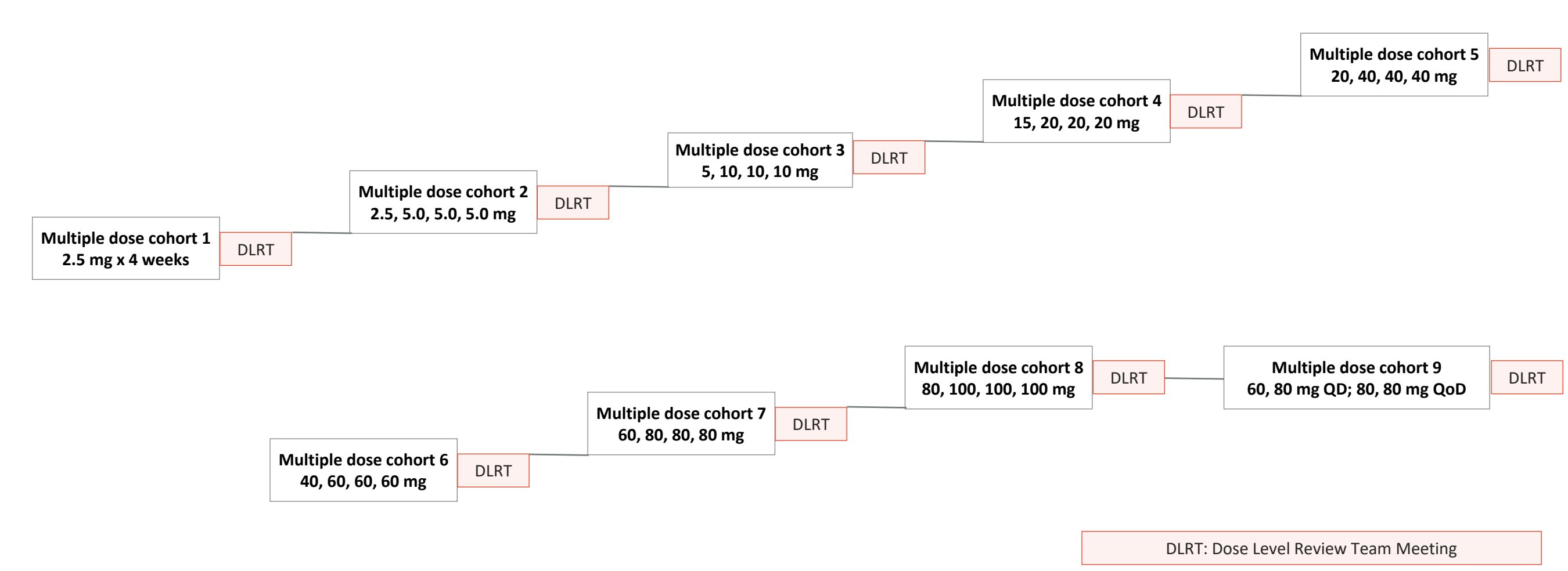
Activation of the glucagon-like peptide 1 (GLP-1) receptor has been shown to decrease glucose, reduce appetite, lower body weight, and improve insulin sensitivity in patients with type 2 diabetes, obesity, or both. Concomitant activation of glucose-dependent insulinotropic polypeptide (GIP) receptors may potentiate the satiety and insulin-sensitizing effects of GLP-1 receptor activation, leading to enhanced clinical benefits. VK2735 is a long-acting dual agonist of the GLP-1/GIP receptors that has shown promise in Phase 1 and 2 studies in healthy subjects and obese patients. We developed an oral tablet formulation that demonstrated encouraging plasma exposures in model studies. We report herein results from a first in human evaluation of this formulation in healthy volunteers with BMI  $\geq 30$ .

## Methods

The Phase 1 trial was a randomized, double-blind, placebo-controlled study in healthy adults with a minimum body mass index of 30 kilograms per meter squared. The primary objective of the study was to evaluate the safety and tolerability of multiple doses of VK2735 administered as an oral tablet once daily for 28 days, and to identify suitable doses for further clinical development. The secondary objective was to evaluate the pharmacokinetics of oral VK2735 in healthy subjects. Exploratory pharmacodynamic measures included assessments of changes in body weight and other metrics.

Statistical analysis: Change and percent change from baseline were analyzed using a mixed model for repeated measures (MMRM) with treatment and visit as factors along with treatment-visit interaction, and baseline weight as a covariate.

## Study Design



## Results

A total of 92 subjects were randomized and received at least one dose of study drug or placebo. Of these, 89 had at least one scheduled post-baseline body weight assessment. Oral VK2735 demonstrated encouraging safety and tolerability following repeated dosing. The majority of observed adverse events (99%) were reported as mild or moderate. All treatment emergent gastrointestinal (GI) related adverse events (100%) were also reported as mild or moderate. Nausea was reported among subjects receiving both VK2735 (32%) and placebo (11%). Among subjects receiving VK2735, all reported nausea (100%) was characterized as mild (0% moderate to severe). Vomiting was reported in 3/73 (4%) VK2735 treated subjects and 0/19 (0%) subjects receiving placebo. At Day 28, cohorts receiving VK2735 demonstrated dose-dependent reductions in mean body weight from baseline, ranging up to 8.2%. Cohorts receiving VK2735 also demonstrated reductions in mean body weight relative to placebo, ranging up to 6.8%. An exploratory assessment of transition from high to low exposure with 80 mg dosing demonstrated promising weight loss trends through 28 days.

## Study Demographics

Mean Baseline Characteristics	Placebo (n=19)	2.5 mg (n=8)	5 mg (n=7)	10 mg (n=6)	20 mg (n=8)	40 mg (n=8)	60 mg (n=9)	80 mg (n=9)	100 mg (n=9)
Age	38	34	29	35	35	33	44	44	44
Sex, M:F (%)	47:53	63:37	43:57	17:83	63:37	25:75	33:67	56:44	44:56
White (%)	68	75	71	100	88	63	89	100	67
Weight (kg)	99	102	97	97	111	89	108	102	103
BMI (kg/m <sup>2</sup> )	36	36	34	36	36	33	37	35	35

Notes: Safety population, includes all randomized subjects who received at least one dose of study drug or placebo.

Table 1. Study demographics

## Mean % Change in Body Weight at Day 28

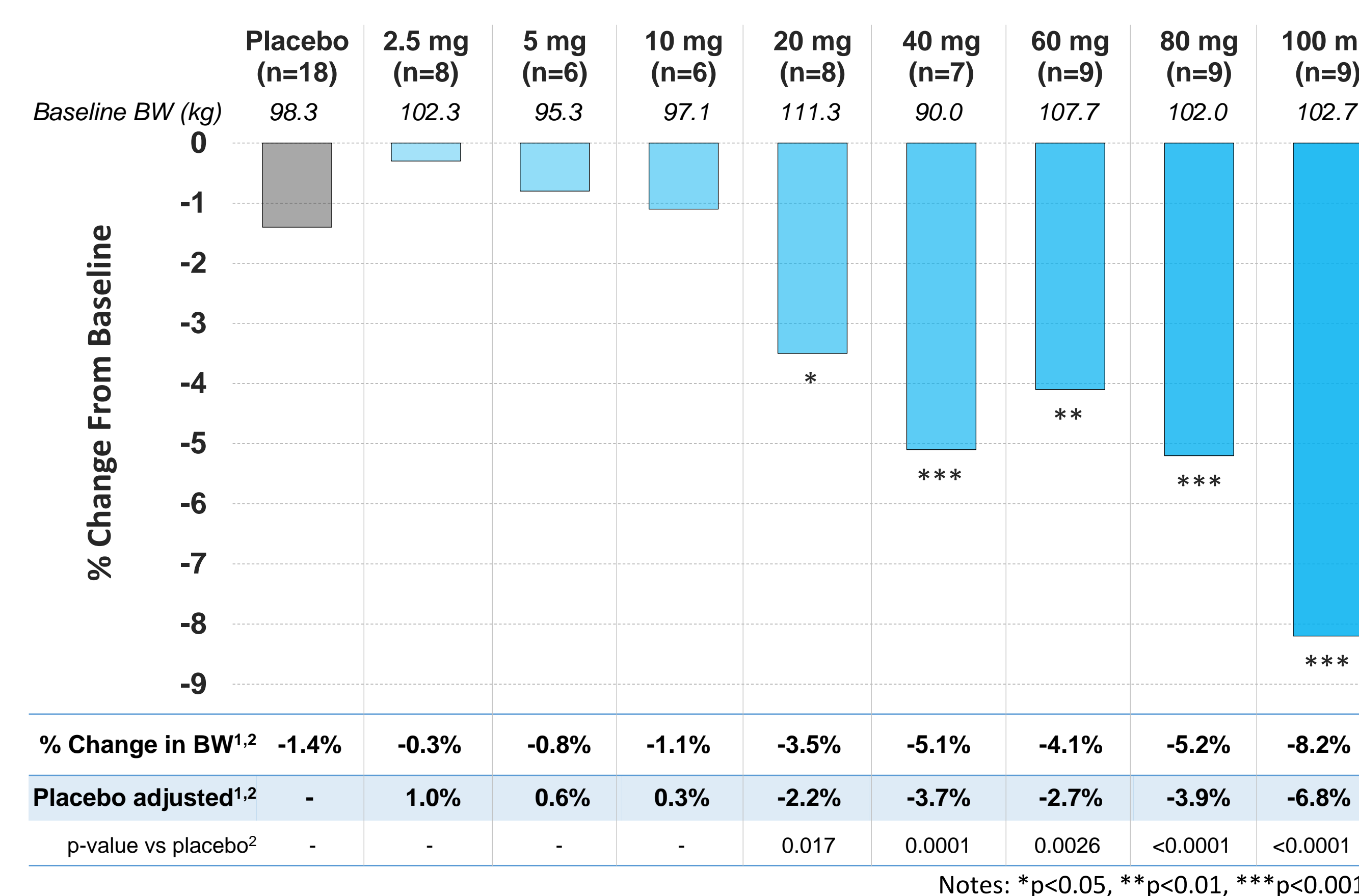


Figure 1. Change in body weight from baseline to Day 28. Efficacy population, includes all randomized subjects who received at least one dose of study drug and had at least one planned post-baseline body weight assessment. Subjects treated with VK2735 were titrated to final doses as indicated: 2.5 mg cohort = 2.5 mg daily x 4 weeks; 5 mg cohort = 2.5 mg daily x 1 wk, 5 mg daily x 3 wks; 10 mg cohort = 5 mg daily x 1 wk, 10 mg daily x 3 wks; 20 mg cohort = 15 mg daily x 1 wk, 20 mg daily x 3 wks; 40 mg cohort = 20 mg daily x 1 wk, 40 mg daily x 3 wks; 60 mg cohort = 40 mg daily x 1 wk, 60 mg daily x 3 wks; 80 mg cohort = 60 mg daily x 1 wk, 80 mg daily x 3 wks; 100 mg cohort = 80 mg daily x 1 wk, 100 mg daily x 3 wks. Subjects were required to have baseline BMI  $\geq 30$  kg/m<sup>2</sup>. Notes: 1) Least squares mean. 2) Two-sided t test using mixed model for repeated measures.

## Change From Baseline Body Weight Over 57 Days

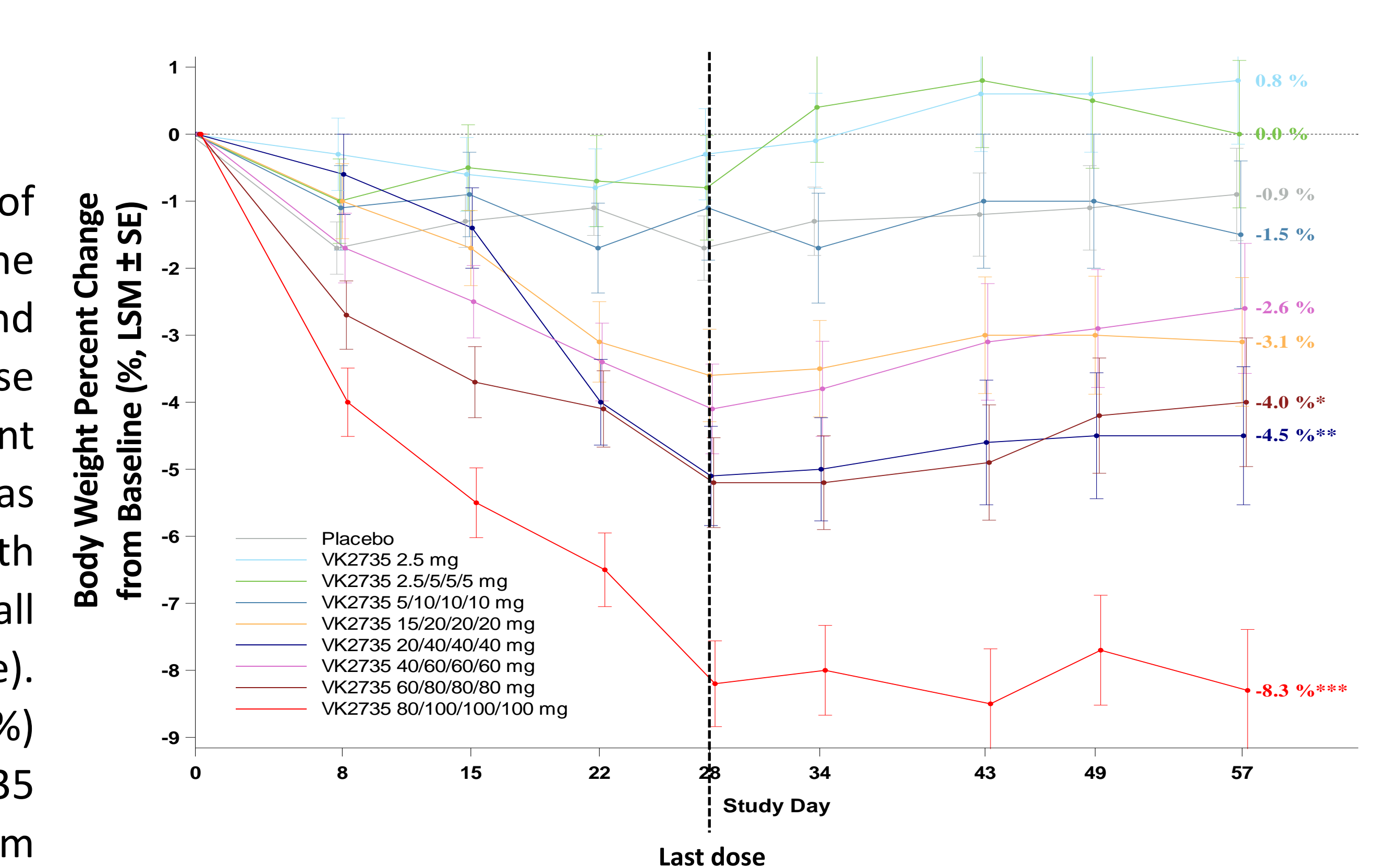


Figure 2. Progressive weight loss observed through Day 28 at doses  $\geq 20$  mg, no plateau. Trends suggests further weight reduction possible with longer dosing period. Following last dose at D28, majority of weight loss maintained through D57.

## Change From Baseline Body Weight Over 28 Days

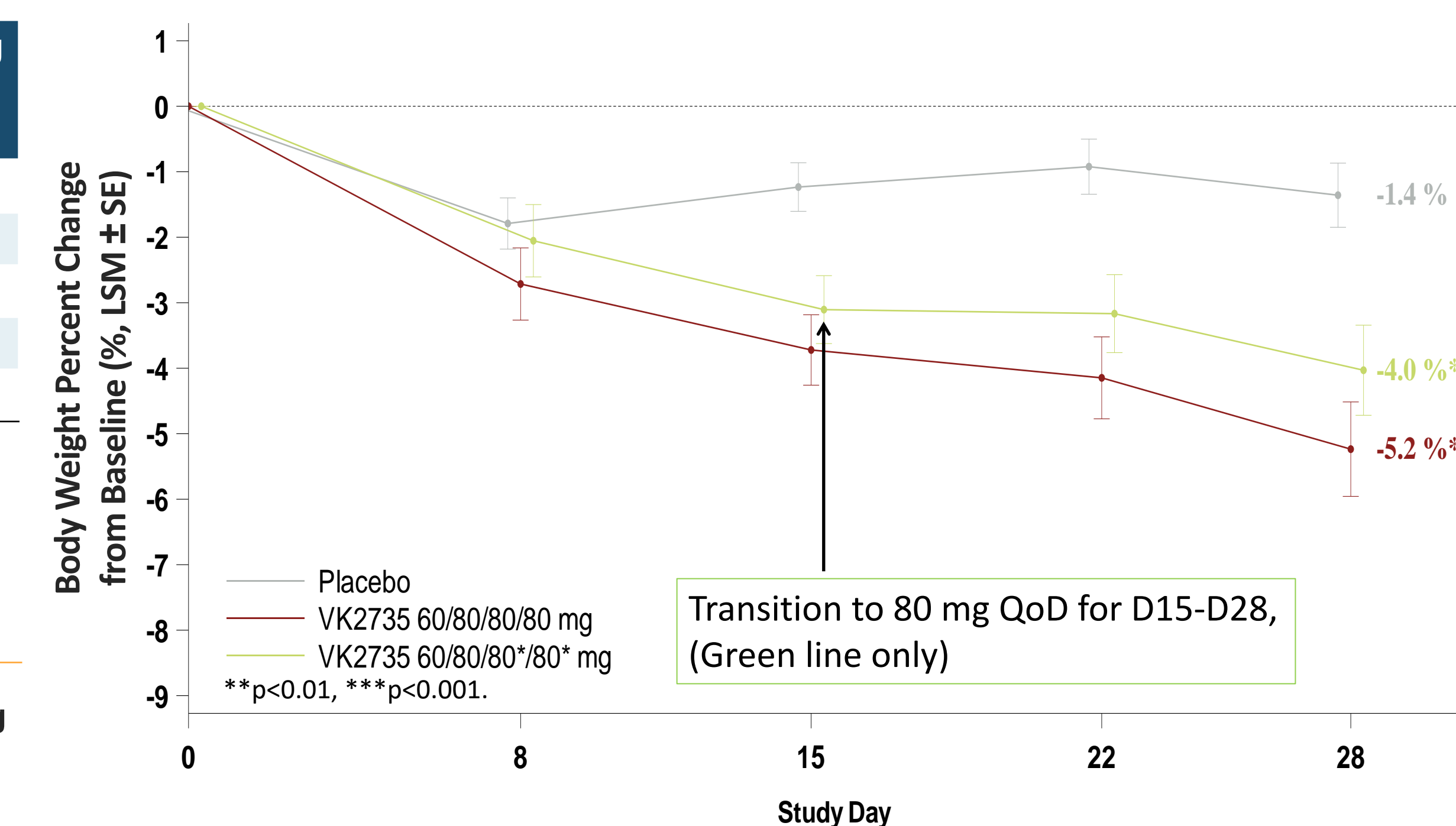


Figure 3. Comparison between high, low exposure 80 mg regimens. Red line: 60 mg daily x 1 wk, 80 mg daily x 3 wks. Green line: 60 mg daily x 1 wk, 80 mg daily x 1 wk, 80 mg QoD x 2 wks.

## Proportion of Subjects With $\geq 3\%$ and $\geq 5\%$ Weight Loss From Baseline at Day 28

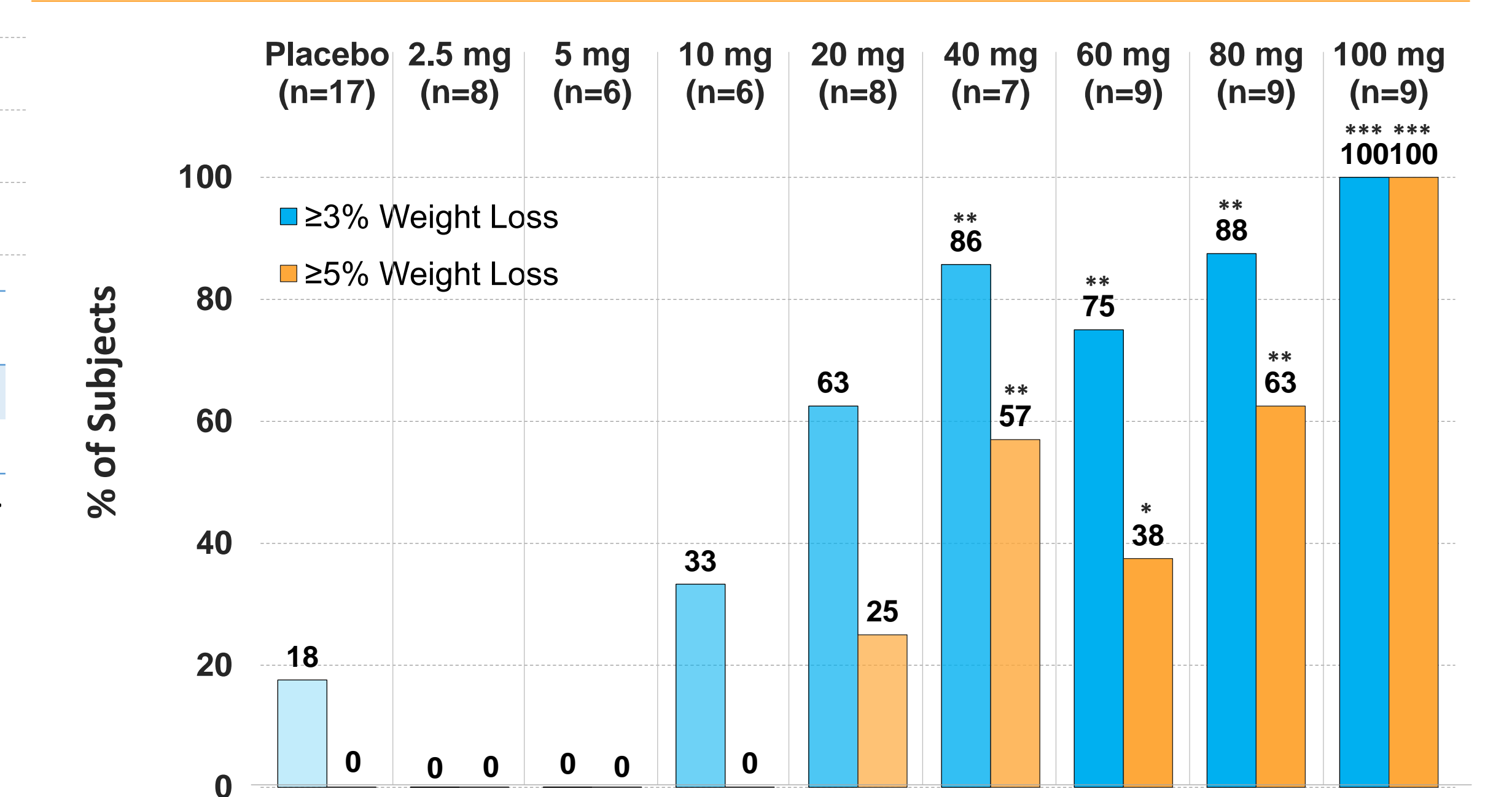


Figure 4. Dose response shows increased proportion of subjects with at least 3% and 5% weight loss with increasing VK2735 dose. Potential to improve with higher dose and/or longer dosing period.

## Change From Baseline Body Weight vs. Satiety

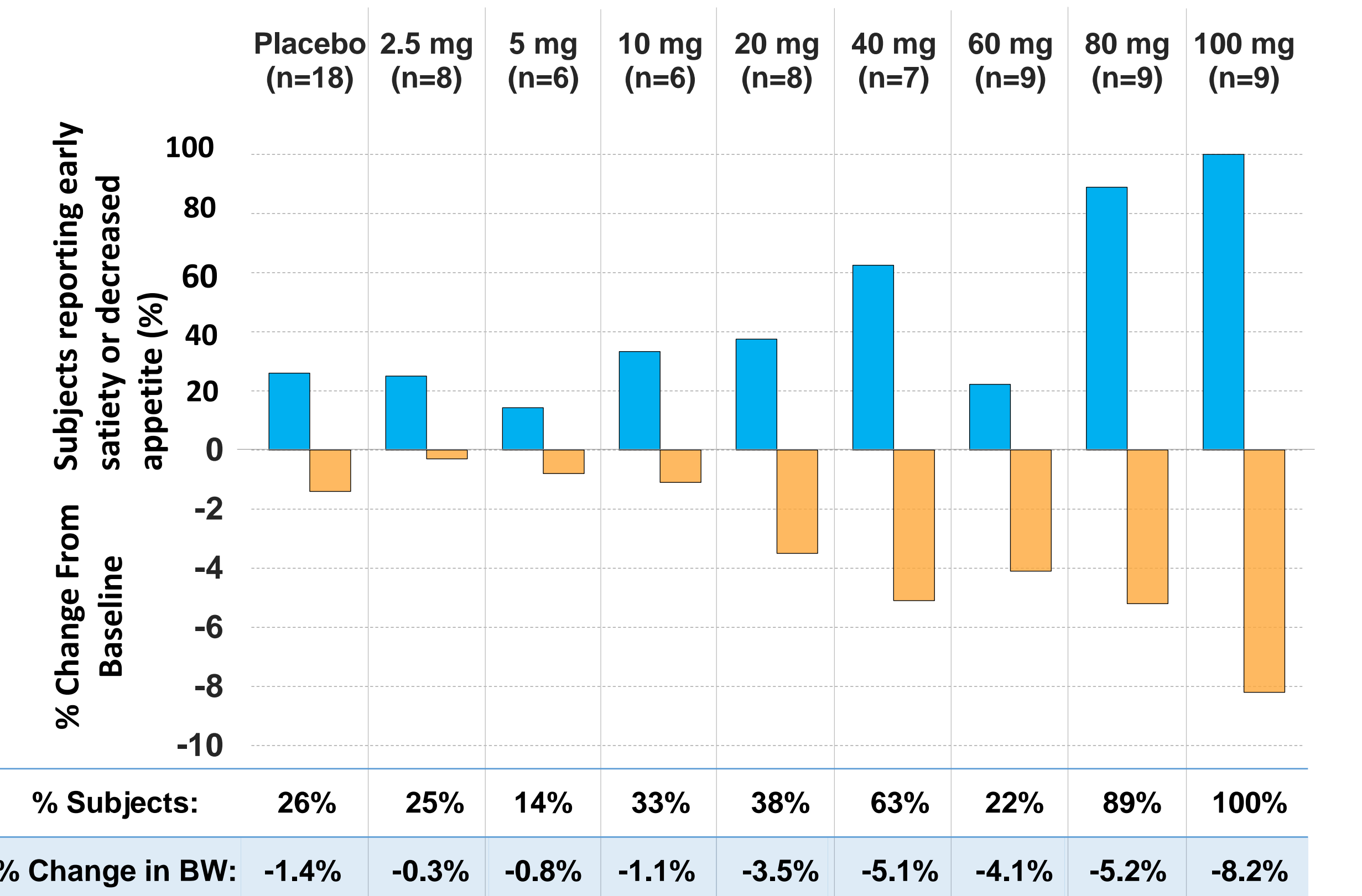


Figure 5. Weight change vs. satiety or decreased appetite. Majority of subjects dosed  $\geq 40$  mg reported reduced appetite/increased satiety, including all subjects in 100 mg cohort.

## Change From Baseline Body Weight vs. AUC

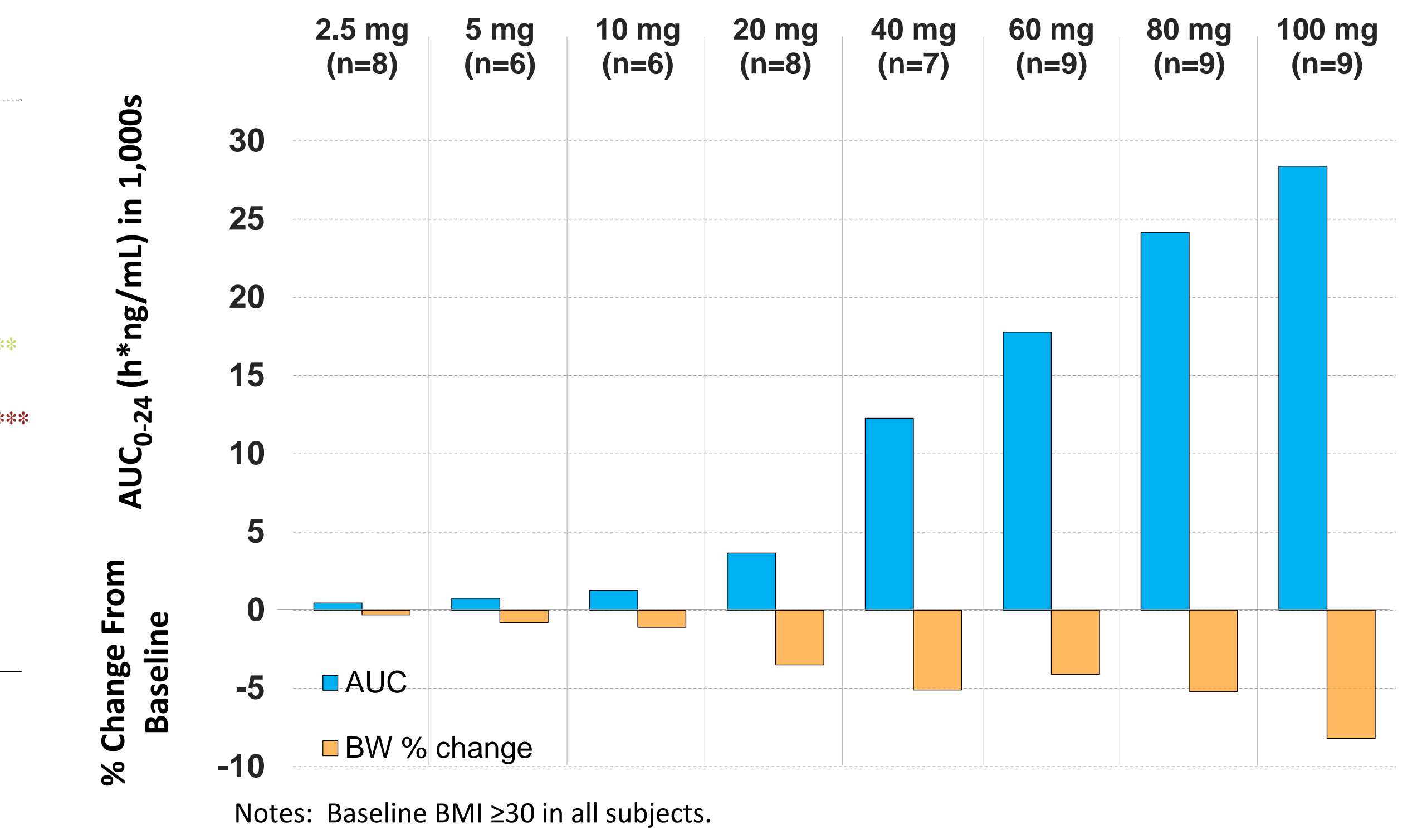


Figure 6. Oral exposures demonstrate linearity with increasing dose.

## GI Tolerability Summary

Common GI related TEAEs	Placebo (n=19)	VK2735 2.5 mg (n=8)	VK2735 5 mg (n=7)	VK2735 10 mg (n=6)	VK2735 20 mg (n=8)	VK2735 40 mg (n=8)	VK2735 60 mg (n=9)	VK2735 80 mg A (n=9)	VK2735 80 mg B (n=9)	VK2735 100 mg (n=9)
GERD	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (11%)	2 (22%)	0 (0%)	0 (0%)
Nausea	2 (11%)	0 (0%)	1 (14%)	0 (0%)	2 (25%)	2 (25%)	2 (22%)	6 (67%)	4 (44%)	6 (67%)
Mild	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)	1 (11%)	1 (11%)
Abdominal pain	2 (11%)	0 (0%)	1 (14%)	1 (17%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	4 (21%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (11%)	1 (11%)	1 (11%)	1 (11%)
Constipation	3 (16%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (33%)	2 (22%)	1 (11%)	4 (44%)

Notes: Safety population, includes all randomized subjects who received at least one dose of study drug or placebo. Subjects treated with VK2735 were titrated to final doses as: 2.5 mg cohort = 2.5 mg daily x 4 weeks; 5 mg cohort = 2.5 mg daily x 1 wk, 5 mg daily x 3 wks; 10 mg cohort = 5 mg daily x 1 wk, 10 mg daily x 3 wks; 20 mg cohort = 15 mg daily x 1 wk, 20 mg daily x 3 wks; 40 mg cohort = 20 mg daily x 1 wk, 40 mg daily x 3 wks; 60 mg cohort = 40 mg daily x 1 wk, 60 mg daily x 3 wks; 80 mg A = 60 mg daily x 1 wk, 80 mg daily x 3 wks; 80 mg B = 60 mg daily x 1 wk, 80 mg daily x 1 wk, 80 mg QoD x 2 wks; 100 mg cohort = 80 mg daily x 1 wk, 100 mg daily x 3 wks. GERD: gastroesophageal reflux disease.

Table 2. GI tolerability summary.

## Adverse Event Summary

Number of subjects	Placebo (n=19)	VK2735 2.5 mg (n=8)	VK2735 5 mg (n=7)	VK2735 10 mg (n=6)	VK2735 20 mg (n=8)	VK2735 40 mg (n=8)	VK2735 60 mg (n=9)	VK2735 80 mg A (n=9)	VK2735 80 mg B (n=9)	VK2735 100 mg (n=9)
Discontinued study early	2 (11%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	1 (13%)	1 (11%)	1 (11%)	0 (0%)	0 (0%)
Treatment emergent adverse events, TEAEs	16 (84%)	6 (75%)	6 (86%)	4 (67%)	6 (75%)	7 (88%)	9 (100%)	9 (100%)	8 (89%)	9 (100%)
Drug related TEAEs	11 (58%)	4 (50%)	4 (57%)	3 (50%)	4 (50%)	7 (88%)	6 (67%)	9 (100%)	7 (78%)	9 (100%)
Serious adverse events	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)

Notes: Safety population, includes all randomized subjects who received at least one dose of study drug or placebo.

Table 3. Adverse event summary. Majority of observed adverse events (99%) were reported as mild or moderate.

## Conclusion

- Oral administration of VK2735 demonstrates encouraging tolerability through 100 mg daily dose level in 28-day study
- Encouraging reductions in body weight reported following 28 days of once-daily dosing
- Durable weight loss observed up to Day 57, 4 weeks after last dose of VK2735
- QD to QoD transition produces similar weight loss and trajectory; suggests reduced exposures may be effective in maintenance setting
- Plasma exposures increase predictably through 100 mg dose level
- Phase 2 trial planned