

Results From the 13-Week VENTURE Phase 2a Study of the GLP-1/GIP Co-Agonist VK2735 in Obese Patients

Naim Alkhouri, MD;¹ Harold E. Bays, MD, FOMA, FTOS, FACC, FNLA, FASPC;² William Kelly Bowman, MD;³ Sureka Bollepalli, MD;⁴ Gary Reiss, MD, MBA;⁵ John Pullman, MD, FACP;⁶ Alpa Patel, MD;⁷ Parke Joseph Hedges, MD, FACOG⁸ and Brian Lian, PhD.⁹

¹Arizona Liver Health; ²Louisville Metabolic and Atherosclerosis Research Center (L-MARC); ³Sensible Healthcare; ⁴Tampa Bay Medical Research; ⁵Tandem Clinical Research; ⁶Mercury Street Medical; ⁷Jacksonville Center for Clinical Research; ⁸Flourish Research-San Antonio; ⁹Viking Therapeutics.

Background

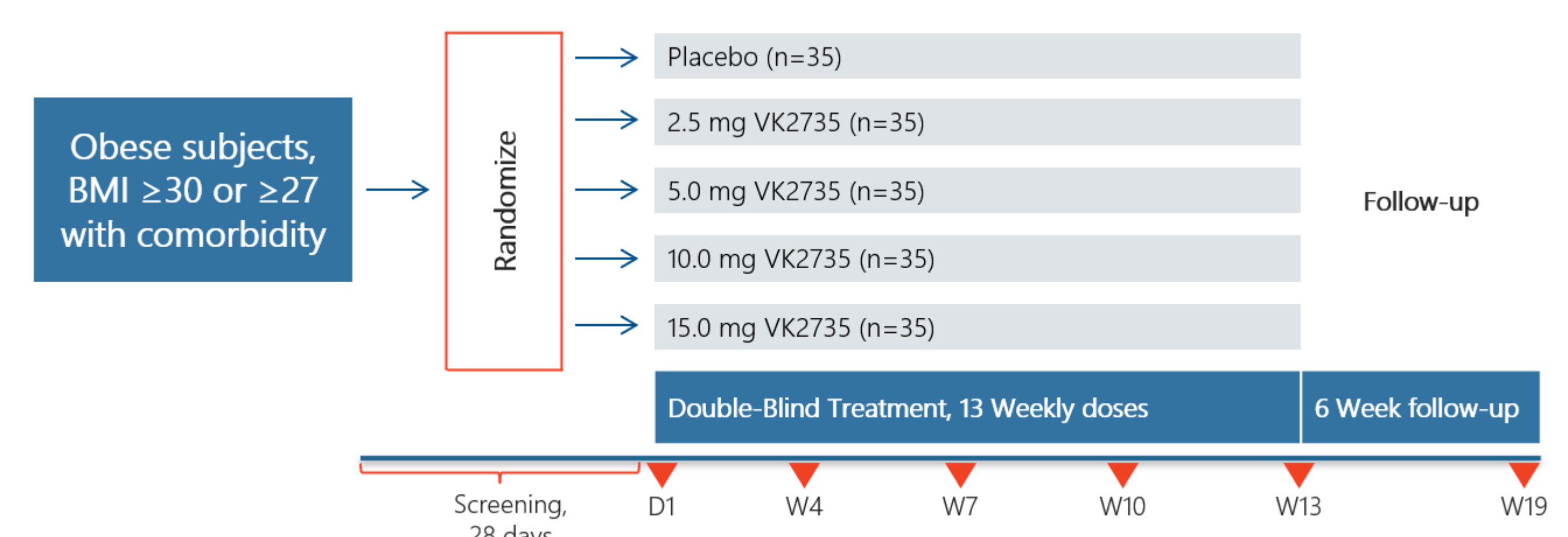
Activation of the glucagon-like peptide 1 (GLP-1) receptor has been shown to decrease glucose, reduce appetite, lower body weight, and improve insulin sensitivity in patients with type 2 diabetes, obesity, or both. Concomitant activation of glucose-dependent insulinotropic polypeptide (GIP) receptors 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 studies in healthy subjects with BMI ≥ 30 . We report herein the results a 13-week Phase 2a study of VK2735 administered by weekly subcutaneous injection.

Methods

The Phase 2 VENTURE trial was a randomized, double-blind, placebo-controlled study intended to evaluate the safety, tolerability, pharmacokinetics, and weight loss efficacy of VK2735, administered subcutaneously, once weekly for 13 weeks. The trial enrolled adults who were obese (BMI ≥ 30 kg/m²), or overweight (BMI ≥ 27 kg/m²) with at least one weight-related comorbid condition. The primary endpoint of the study was the percent change in body weight from baseline to Week 13 among patients treated with VK2735 as compared with placebo. Secondary and exploratory endpoints evaluated a range of additional safety and efficacy measures.

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



Patients treated with VK2735 were titrated to final doses as indicated: 2.5 mg cohort = 2.5 mg x 13 weeks; 5 mg cohort = 2.5 mg x 3 wks, 5 mg x 10 wks; 10 mg cohort = 2.5 mg x 3 wks, 5 mg x 3 wks, 7.5 mg x 3 wks, 10 mg x 4 wks; 15 mg cohort = 5 mg x 3 wks, 7.5 mg x 3 wks, 10 mg x 3 wks, 15 mg x 4 wks.

Results

A total of 175 patients were randomized and received at least one dose of study drug or placebo. Patients receiving weekly doses of VK2735 demonstrated statistically significant reductions in mean body weight after 13 weeks, ranging up to 14.7% from baseline. Patients receiving VK2735 also demonstrated statistically significant reductions in mean body weight relative to placebo, ranging up to 13.1%. Statistically significant differences compared to both baseline and placebo were observed for all doses starting at Week 1 and continuing throughout the 13-week treatment period. Reductions in body weight were progressive through the course of the study, with no plateau observed at 13 weeks. VK2735 demonstrated encouraging safety and tolerability following 13 weeks of once-weekly dosing. Among patients receiving VK2735, the majority (92%) reported drug related TEAEs as mild or moderate in severity.

Demographics

Mean Baseline Characteristics	Placebo (n=34)	2.5 mg (n=35)	5.0 mg (n=35)	10.0 mg (n=35)	15.0 mg (n=35)
Age	48	50	52	47	51
Sex, M:F (%)	18:82	23:77	34:66	34:66	23:77
White (%)	77	80	89	74	80
Weight (kg)	105	103	98	103	101
BMI (kg/m ²)	39	38	36	37	37

Table 1. Study demographics, efficacy population. All patients required to have BMI ≥ 30 , or ≥ 27 and one additional weight-related comorbidity.

Mean % Change in Body Weight After 13 Weeks^{1,2}

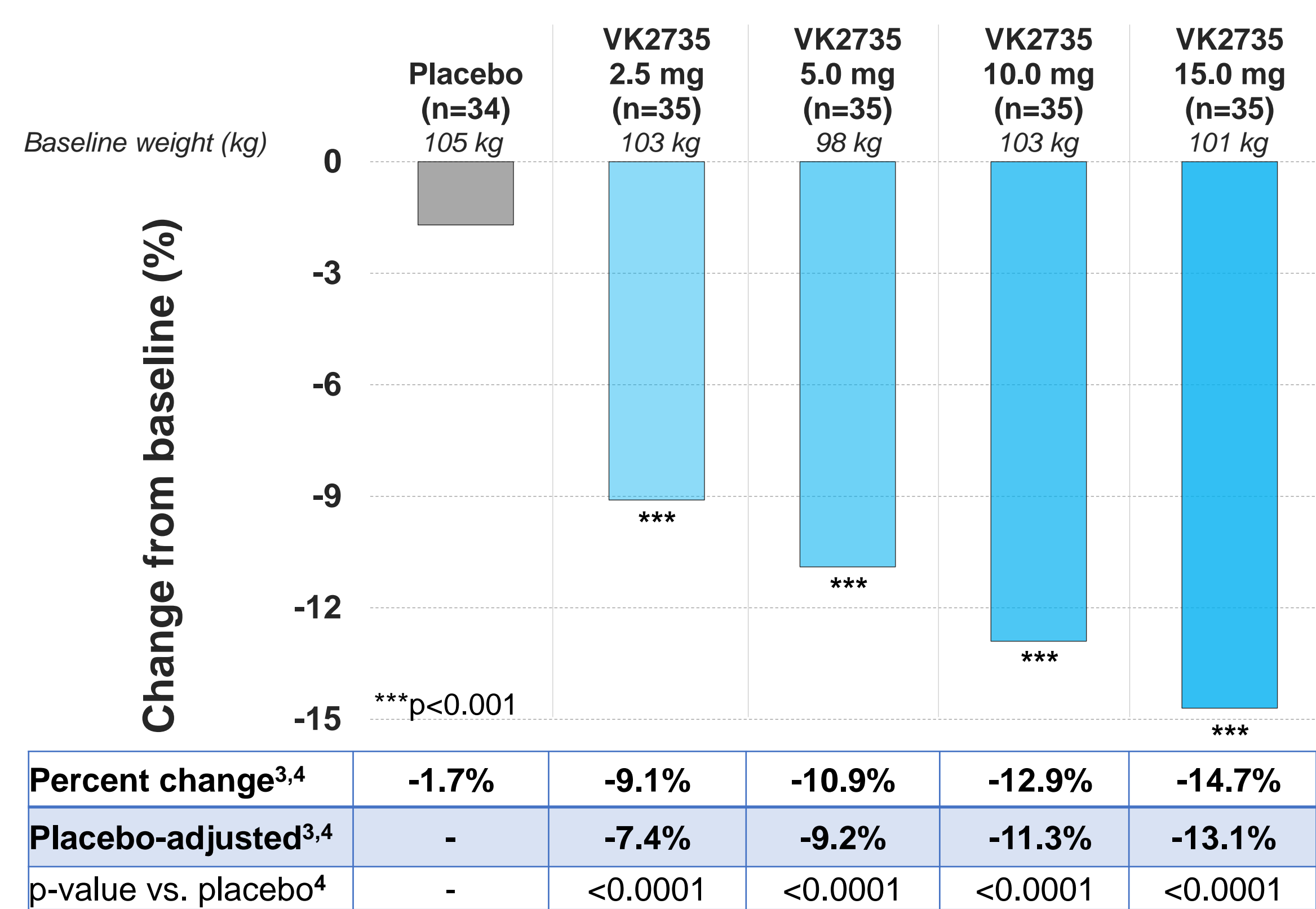


Figure 1 and Table 2. Notes: 1) Efficacy population, includes all randomized patients who received at least one dose of study drug or placebo and had a valid baseline and post-baseline body weight assessment. 2) Patients treated with VK2735 were titrated to final doses as indicated: 2.5 mg cohort = 2.5 mg x 13 weeks; 5 mg cohort = 2.5 mg x 3 wks, 5 mg x 10 wks; 10 mg cohort = 2.5 mg x 3 wks, 5 mg x 3 wks, 7.5 mg x 3 wks, 10 mg x 4 wks; 15 mg cohort = 5 mg x 3 wks, 7.5 mg x 3 wks, 10 mg x 3 wks, 15 mg x 4 wks. 3) Least squares mean. 4) Two-sided t test using mixed model for repeated measures.

Change From Baseline Body Weight Over 13 Weeks

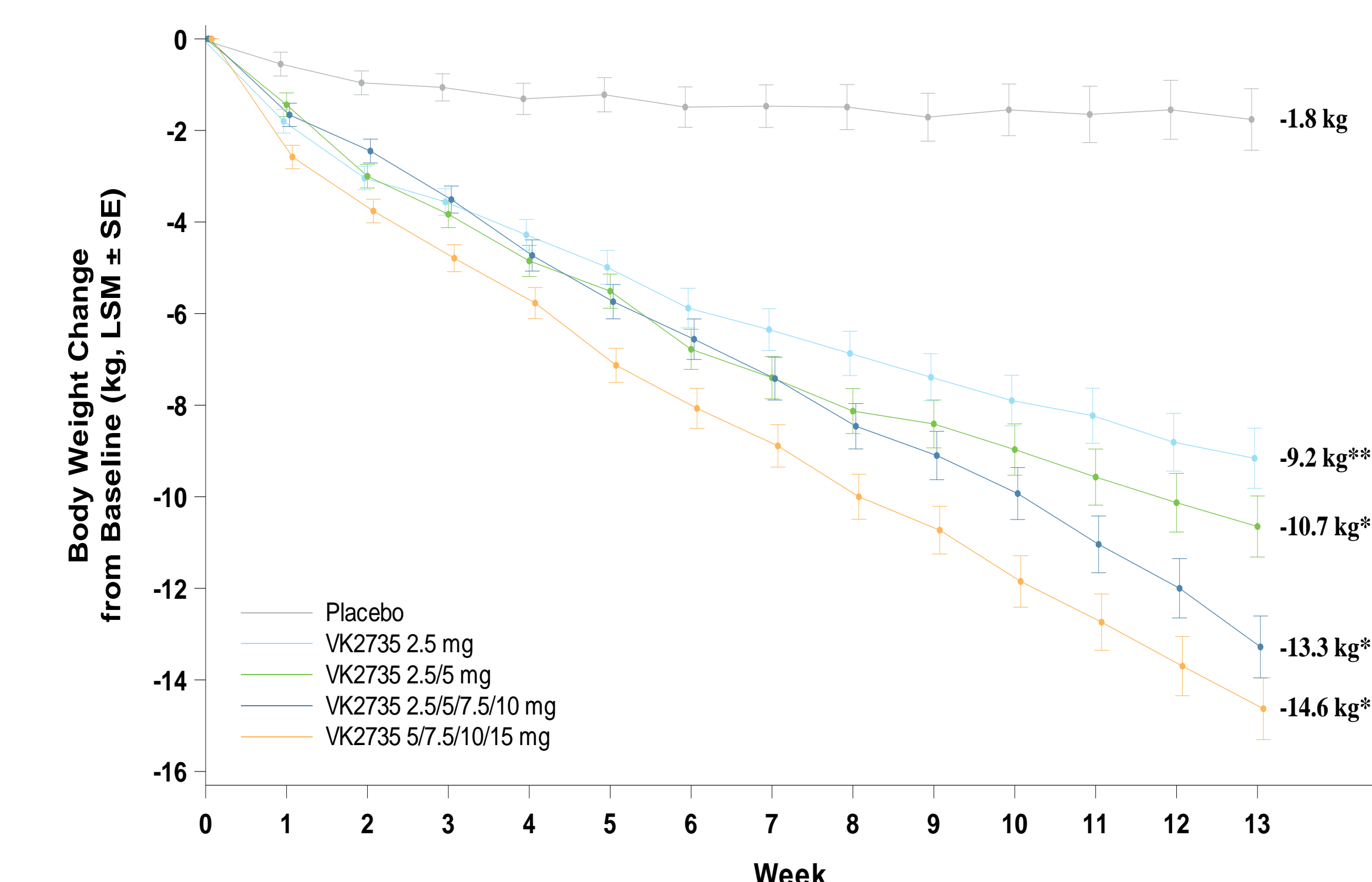


Figure 2. Progressive weight loss observed in all VK2735 dosing cohorts. All doses statistically significant vs. placebo starting in Week 1 and maintained through Week 13. Dose dependent effects observed. No evidence of plateau suggests further weight reduction possible with continued dosing.

Patients Reporting $\geq 10\%$ Weight Loss at 13 Weeks

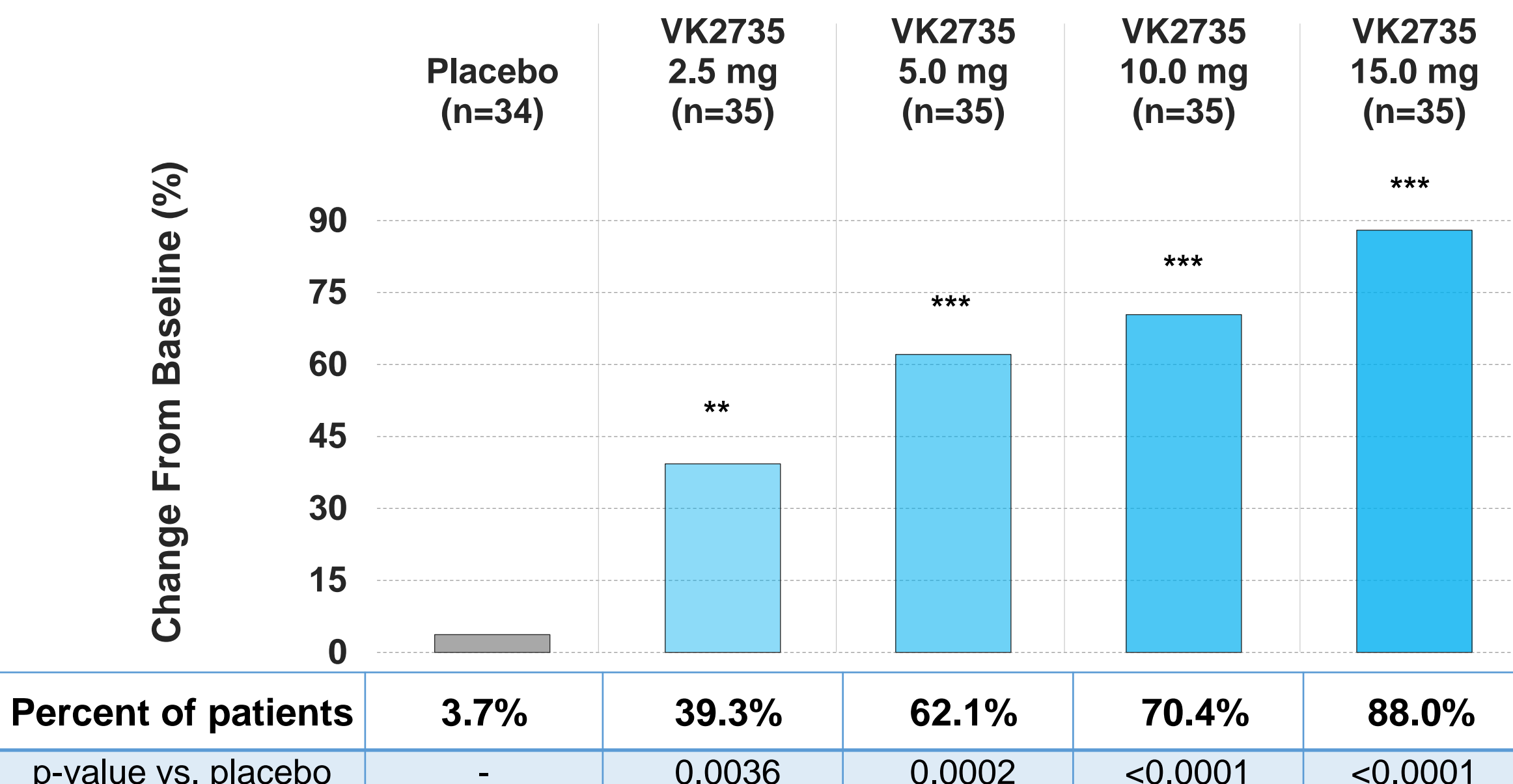
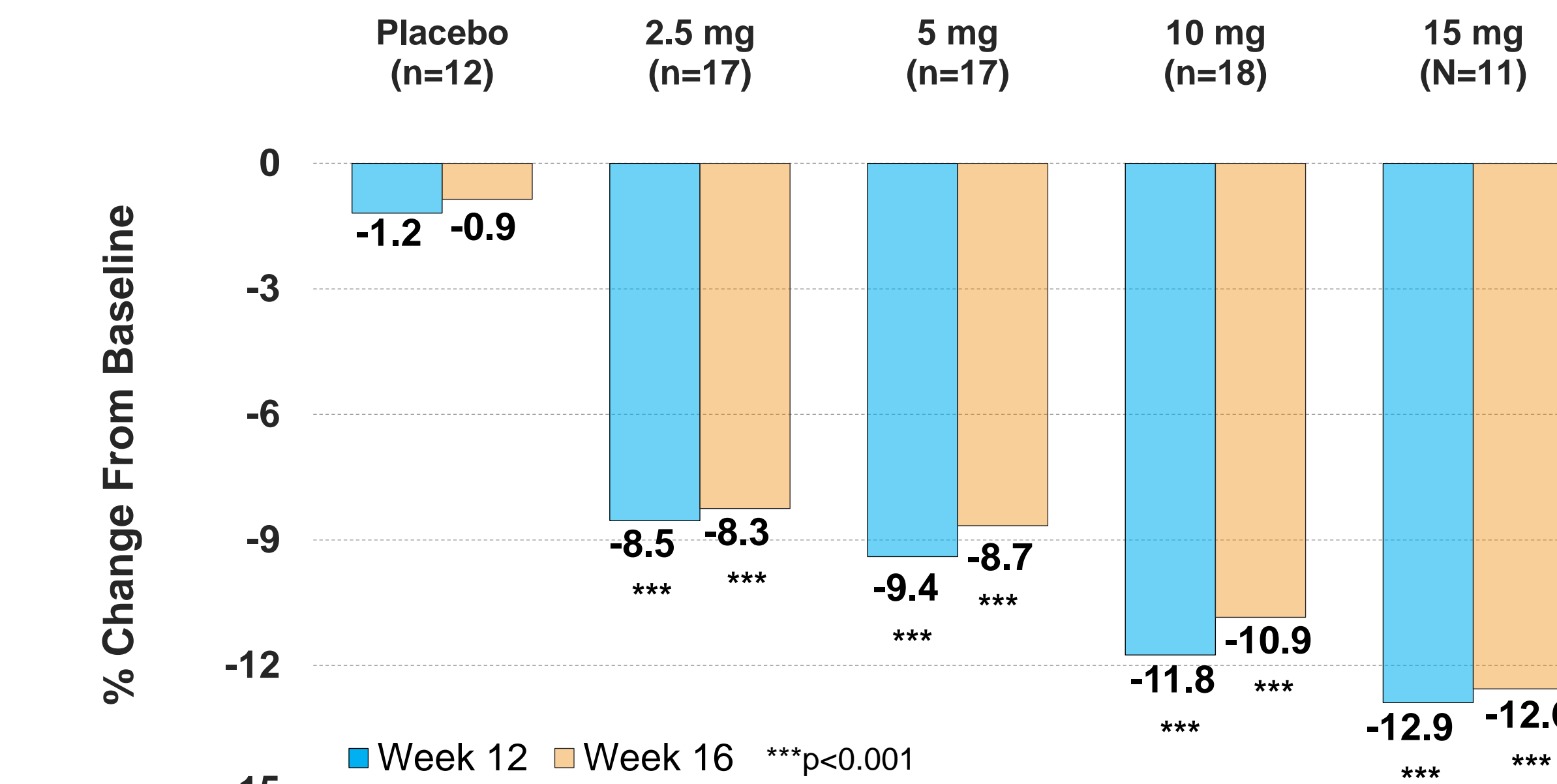


Figure 3 and Table 3. Up to 88% of patients experienced $\geq 10\%$ weight loss.

Mean % Change in Body Weight After 12, 16 Weeks



Proportion of Weight Loss Maintained, PK Subsets

Study Week	Weeks from Last Dose	2.5 mg (n=17)	5.0 mg (n=17)	10.0 mg (n=18)	15.0 mg (n=11)	Combined VK2735 arms
16 Weeks	4 Weeks	98%	92%	92%	96%	94%
19 Weeks	7 Weeks	91%	82%	75%	87%	83%

Figure 4 and Table 4. Majority of weight loss maintained at 4- and 7-weeks following last dose of study drug.

VK2735 Accumulation Through 13 Weekly Doses

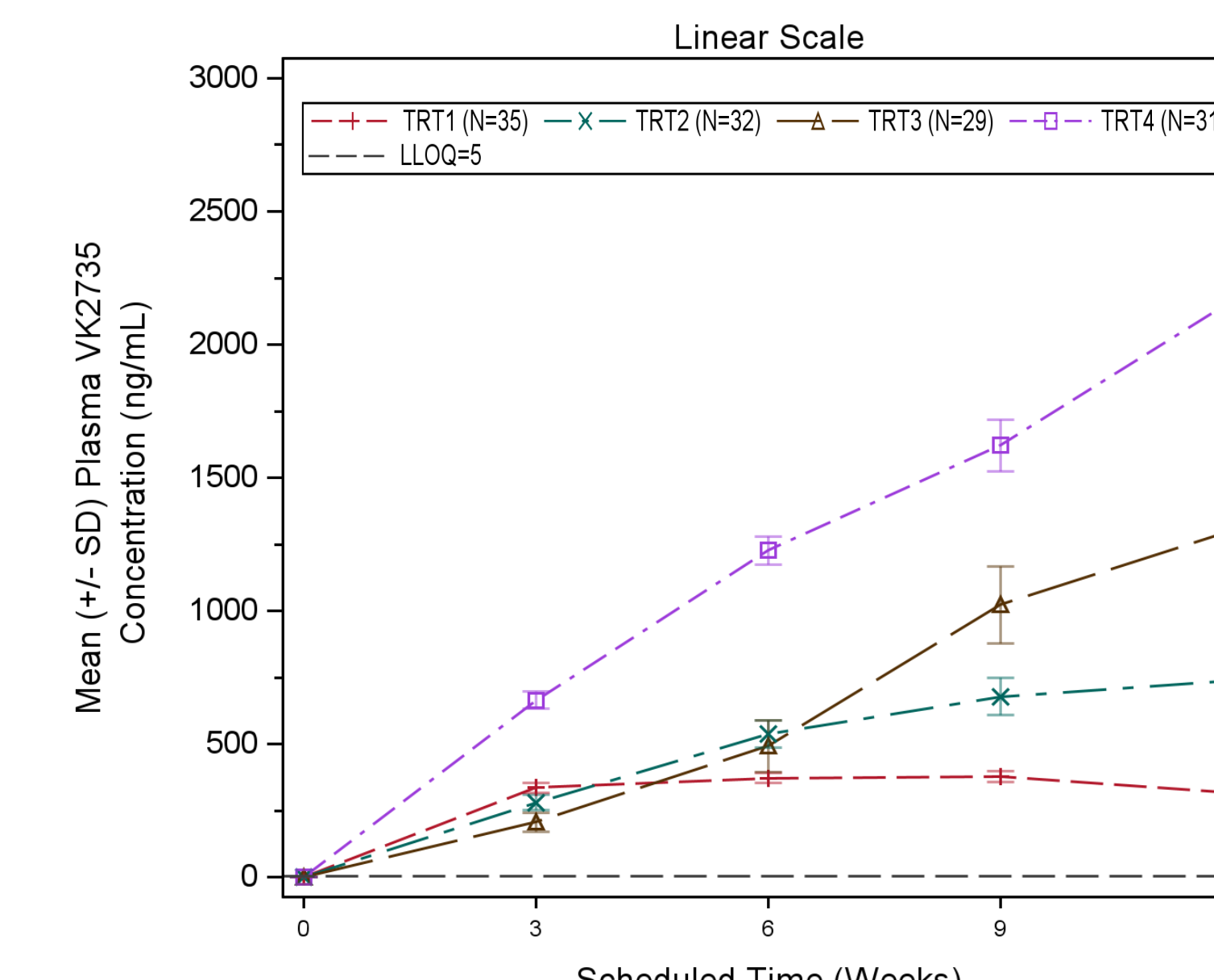


Figure 5. VK2735 plasma concentrations through 13 weekly doses.

VK2735 Plasma Levels Through 7-Week Follow-up

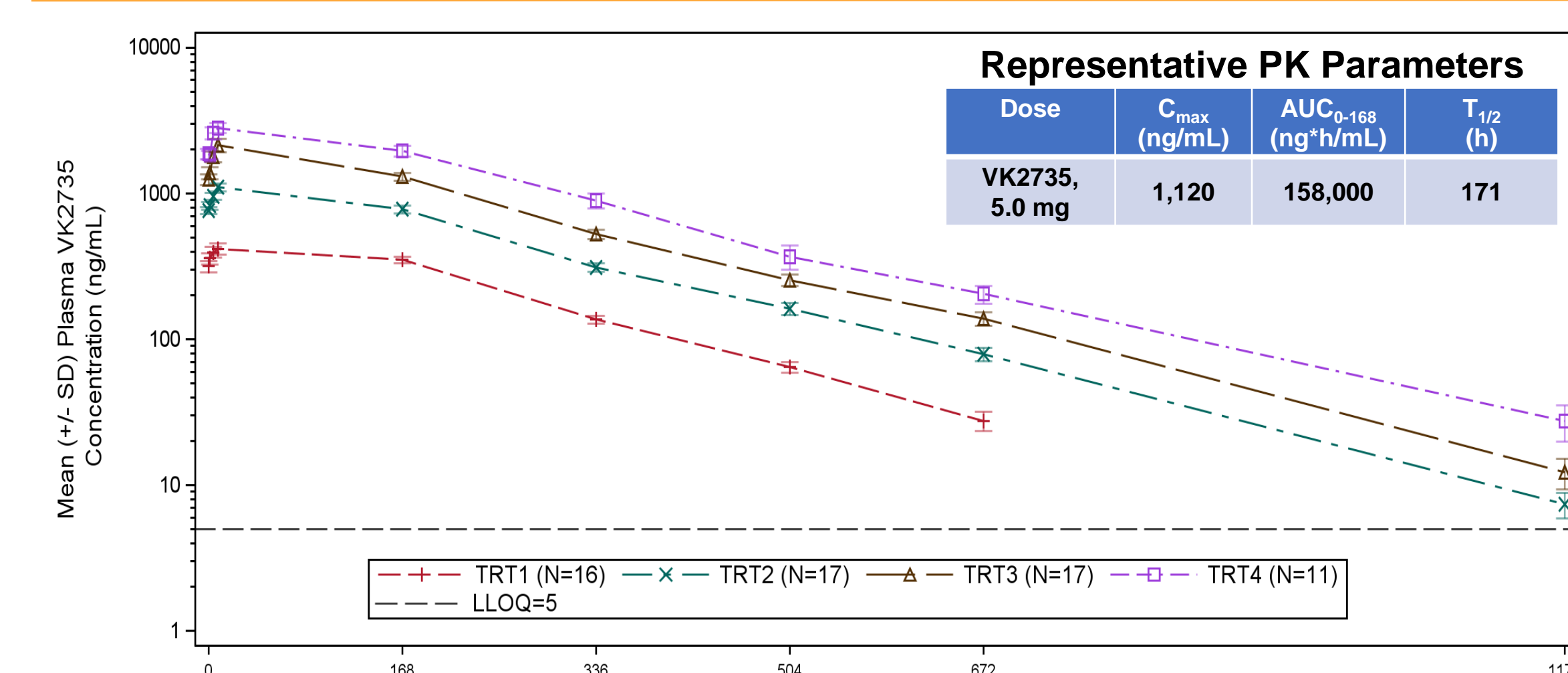


Figure 6. Plasma levels of VK2735 through 7 weeks of follow-up.

Summary of TEAEs and GI Tolerability

Number of patients reporting (%)	Placebo (n=35)	VK2735 2.5 mg (n=35)	VK2735 5.0 mg (n=35)	VK2735 10.0 mg (n=35)	VK2735 15.0 mg (n=35)	VK2735 Combined (n=140)
Discontinued treatment early	5 (14%)	2 (6%)	4 (11%)	5 (14%)	7 (20%)	18 (13%)
Discontinued study early	2 (6%)	1 (3%)	1 (3%)	2 (6%)	2 (6%)	6 (4%)
Overall TEAEs	24 (69%)	25 (71%)	31 (89%)	30 (86%)	32 (91%)	118 (84%)
Drug related TEAEs	16 (46%)	21 (60%)	27 (77%)	26 (74%)	30 (86%)	104 (74%)
Drug related TEAEs leading to study discontinuation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (1%)
Common GI related TEAEs	Placebo (n=35)	VK2735 2.5 mg (n=35)	VK2735 5.0 mg (n=35)	VK2735 10.0 mg (n=35)	VK2735 15.0 mg (n=35)	VK2735 Combined (n=140)
GERD	1 (3%)	2 (6%)	5 (14%)	4 (11%)	6 (17%)	17 (12%)
Nausea	7 (20%)	6 (17%)	11 (31%)	9 (26%)	15 (43%)	41 (29%)
Mild	0 (0%)	3 (9%)	5 (14%)	4 (11%)	7 (20%)	19 (14%)
Moderate	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%)
Vomiting	0 (0%)	3 (9%)	6 (17%)	6 (17%)	10 (29%)	25 (18%)
Abdominal pain	1 (3%)	1 (3%)	2 (6%)	1 (3%)	2 (6%)	6 (4%)
Diarrhea	3 (9%)	11 (31%)	6 (17%)	7 (20%)	4 (11%)	28 (20%)
Constipation	4 (11%)	7 (20%)	10 (29%)	9 (26%)	10 (29%)	36 (26%)
Decreased appetite	0 (0%)	2 (6%)	5 (14%)	9 (26%)	6 (17%)	22 (16%)

Table 5. Summary of TEAEs and GI related AEs, safety population. Includes all randomized patients who received at least one dose of study drug or placebo.

Timecourse of GI Adverse Events

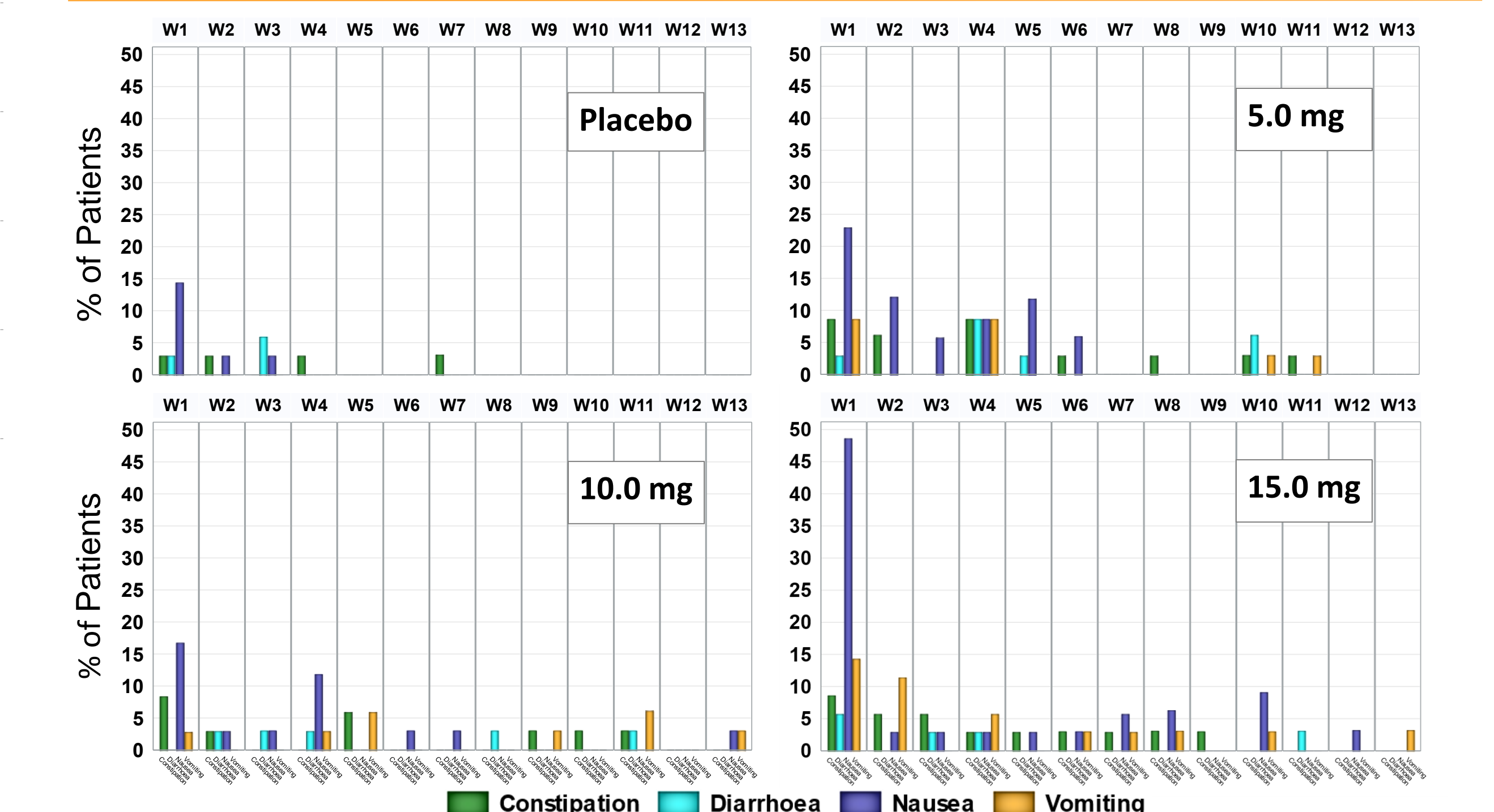


Figure 7. Timecourse of GI related adverse events. Safety population; includes all randomized patients who received at least one dose of study drug or placebo.

Summary Vital Signs at Week 13

Marker	Placebo	VK2735 2.5 mg	VK2735 5.0 mg	VK2735 10.0 mg	VK2735 15.0 mg
Heart rate (bpm)	Baseline 65.7	63.5	66.9	64.3	63.9
Mean Change at Week 13	4.4	3.8	5.0	10.8	7.1
Systolic blood pressure (mmHg)	Baseline 125.1	126.2	128.6	122.1	123.4
Mean Change at Week 13	-4.4	-7.4	-8.8	-5.4	-9.6
Diastolic blood pressure (mmHg)	Baseline 80.9	81.6	82.9	78.5	78.4
Mean Change at Week 13	-2.2	-3.7	-5.5	-1.5	-4.3

Table 6. Summary of vital signs, safety population.

Conclusion

- VK2735 dosed weekly by subcutaneous injection for 13 weeks led to weight loss of up to 14.7% from baseline
- Progressive weight loss observed; no plateau at 13 weeks
- >90% of weight reduction maintained 4 weeks post-final dose
- PK, exposure profile suggests monthly dosing may be feasible
- Promising tolerability, 92% of drug related TEAEs reported as mild to moderate
- Mild GI AE profile consistent with incretin axis activation; generally waned following initial exposures
- Phase 3 clinical trials are planned