Obesity

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Clinical Trials and Investigations

Weekly Subcutaneous VK2735, a GIP/GLP-1 Receptor Dual Agonist, for Weight Management: Phase 2, Randomized, 13-Week VENTURE Study

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Keywords: antiobesity | GLP-1 | obesity treatment | weight loss | weight management

ABSTRACT

Objective: This study aimed to determine doses of VK2735, a novel glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GLP-1/GIP) receptor dual agonist, that are effective for weight loss over 13 weeks of treatment.

Methods: VENTURE was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study of weekly subcutaneous VK2735 in adults with obesity or overweight and ≥1 weight-related comorbidity. Participants with diabetes mellitus were ineligible. The primary endpoint was percent change from baseline in body weight at Week 13. Secondary efficacy endpoints were observed and change from baseline weight loss and the proportion of participants losing ≥5% and ≥10% of baseline weight.

Results: Study was conducted between August 2023 and February 2024. Mean weight reduction with active treatment ranged from 9.2 kg (2.5 mg dose) to 14.6 kg (15 mg dose), corresponding to 9.1% and 14.7% weight reductions, respectively; the placebo group had a 1.8 kg (1.7%) reduction. In the active treatment groups, 93% (130/140) of participants had a ≥5% weight reduction, compared with 12% (4/34) of participants with placebo treatment. The common adverse events (AEs) were gastrointestinal, which decreased in reported frequency after dose titration to steady state.

Conclusions: All subcutaneous doses of VK2735 significantly reduced body weight. The AE profile of VK2735 was primarily gastrointestinal, with decreased reported frequency upon continued use.

Trial Registration: ClinicalTrials.gov identifier NCT06068946

1 | Introduction

Excess body fat represents one of the most prevalent and fastest growing chronic health disorders in the United States and worldwide [1–3]. Overweight and obesity increase morbidity and mortality [4, 5] and contribute to type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, strokes, sleep apnea, some cancers, and arthritis, as well as psychosocial complications [6–9]. Interventional and epidemiological studies support that reduction of excess body weight reduces morbidity and mortality, and that this reduction is correlated with the magnitude of weight loss [10, 11]. Weight loss of as little as 5%–10% is associated

Study Importance

- What is already known?
  - Obesity is a multisystem disease that is increasingly prevalent in the United States and globally.
  - Lifestyle modification alone has demonstrated limited success in achieving clinically meaningful weight loss; alternative treatments that enable sustained weight loss are necessary to decrease the prevalence of obesity/overweight and associated weight-related comorbidities.
- What does this study add?
  - Results from VENTURE, a phase 2 study of VK2735 in participants with obesity or overweight with at least one weight-related comorbidity, demonstrated clinically meaningful weight loss with no indication of a plateau at Week 13.
  - VK2735 also demonstrated encouraging safety and tolerability throughout the 13-week treatment period, with the majority of drug-related treatment-emergent adverse events being categorized as mild or moderate.
- How might these results change the direction of research or the focus of clinical practice?
  - VK2735, a dual incretin receptor agonist, has demonstrated notable efficacy and tolerability in this phase 2 trial and may be an effective option in the treatment of individuals with overweight or obesity.

with a reduction in new onset type 2 diabetes and some cancers and improvements in sleep apnea, hypertension, dyslipidemia, hyperglycemia, osteoarthritis of the knee, and polycystic ovary disease [12–16].

The health benefits of effective treatment of overweight and obesity can lead to a potential reduction in monetary costs. Following a 5% reduction of body mass index (BMI), measured as weight in kilograms divided by height in meters squared (kg/m^2), adults with a baseline BMI of $30\,kg/m^2$ are estimated to spend 7% less on health care, with the magnitude of benefit correlating to the magnitude of weight reduction [17–19]. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GIP/GLP-1) receptor agonist approved by the FDA for treatment of type 2 diabetes and obesity. Clinical trials support that tirzepatide favorably affects glycemic control, lipid profiles, and blood pressure [20–22]. Additional treatment options with favorable safety profiles and easier dosing could expand access and support treatment persistence.

VK2735 binds with high affinity to both the GLP-1 receptor (IC50: 188 nM) and GIP receptor (IC50: 325 nM) (unpublished data, Viking Therapeutics, Inc.). The VK2735 peptide incorporates the activities of both incretins and contains a side chain that imparts an extended half-life when administered as a subcutaneous injection. Preclinical and phase 1 studies indicate VK2735 has a favorable efficacy, safety, and tolerability profile (unpublished data, Viking Therapeutics, Inc.). The VENTURE study was a 13-week, dose-ranging study designed to provide preliminary efficacy and safety data for subcutaneous VK2735 as a treatment for obesity to inform phase 3 study design.

2 | Methods

2.1 | Study Design and Randomization

VENTURE was a phase 2, 13-week, randomized, double-blind, placebo-controlled, parallel-arm, dose-finding study conducted in 20 sites in the United States. The protocol was reviewed and approved by the institutional review boards or ethics committees of each participating institution. The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH Good Clinical Practice (GCP) Guidelines, and all applicable laws and regulations.

The total study duration was 23 weeks, comprising a 4-week screening period, a 13-week treatment period, and an approximately 6-week safety follow-up period (Figure S1). Participants who met eligibility criteria were randomized to one of four VK2735 weekly subcutaneous injection treatment groups (2.5, 5.0, 10, or 15 mg) or the matched placebo injection group in a 1:1:1:1:1 ratio on day 1 (Figure S1 and Table S1). Placebo injections were matched for volume. Titration to final dose was conducted as shown in Figure S1 for the active treatment groups.

All participants were encouraged to exercise for approximately 150 min per week and reduce daily intake by 500 kcal. Instructional materials were provided at Week 0 (i.e., randomization), and counseling sessions were conducted at study sites at Week 3, Week 6, and Week 9 (Table S1). Participants were asked to fast for no fewer than 6 h prior to lipid and chemistry panel blood collections. On study days with PK sample collection scheduled, participants were similarly asked to fast for no less than 6 h. Fasting was not otherwise required for dosing. Fasting was defined as no food or beverage intake other than water.

2.2 | Participants

Eligible participants were over the age of 18 years, with BMI $\geq 30\,kg/m^2$ or BMI $\geq 27\,kg/m^2$ and at least one weight-related comorbid condition (treated or untreated). Weight-related comorbid conditions include hypertension, dyslipidemia, obstructive sleep apnea, and cardiovascular disease. Participants with BMI $> 50\,kg/m^2$ or with certain medical conditions, including diabetes, were not eligible. Full inclusion and exclusion criteria are contained in the online Supporting Information.

Participants provided written consent to participate in the study at the first visit, before the initiation of any study-related procedure, after being informed of the purpose of the study and that their participation was voluntary.

All participants were centrally assigned to a randomized study intervention using an Interactive Web Response System (IWRS). Before the study was initiated, the log-in information and directions for the IWRS were provided to each site. Each participant was provided with a unique screening number after

documentation that informed consent had been completed. Once deemed eligible for enrollment in the study, participants were assigned a sequential randomization number prior to first dosing. The investigators and study staff were blinded to each participant's assigned study intervention throughout the course of the study. Subcutaneous injections were matched for volume for placebo and active treatment groups.

The randomized population includes all participants who were randomized into the study. The modified intent-to-treat (mITT) population is defined as all participants within the ITT population who had at least one baseline and post-baseline body weight assessment and received at least one dose of study drug. The safety population is defined as all randomized participants who received at least one dose of study drug.

2.3 | Objectives and Outcome Measures

The main objectives of the VENTURE study were to evaluate the safety, tolerability, and weight loss efficacy of VK2735. The primary endpoint was percent (relative) change from baseline to Week 13 in body weight. Secondary efficacy endpoints were observed and change from baseline to Week 13 in body weight and the proportion of participants losing ≥5% and 10% of baseline weight at Week 13. The proportion of participants losing ≥15% of baseline weight was an exploratory objective. A schedule of assessments (Table S1) and a full list of study endpoints (Table S2) are provided in the online Supporting Information.

Safety endpoints included incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest. Changes in vital signs and the proportion of participants with anti-drug antibodies were also evaluated.

Key exploratory endpoints included effects of VK2735 on glycemic status, cardiometabolic parameters, and anthropometric parameters. Categories of glycemic control were defined by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) as: normoglycemic = FPG < 100 mg/dL and HbA1c < 5.7%, prediabetes = FPG 100–125 mg/dL or HbA1c 5.7%–6.4%, and diabetes = FPG > 125 mg/dL or HbA1c > 6.4%.

2.4 | Statistical Analyses

Sample size of 29 in active and placebo groups was estimated to achieve 84% power to reject the null hypothesis of equal means when the population mean difference (percent change from baseline) between treatment groups is 2.6% with standard deviations (SD) of 3.3% for each treatment group with a significance level (alpha) of 0.05 using a two-sided, two-sample *t*-test.

Percent change from baseline was analyzed using a mixed model for repeated measures (MMRM) approach with baseline treatment, visit, and treatment*visit interaction as factors and baseline weight as a covariate. If there were multiple weights on a particular day, the average of measurements on that day was

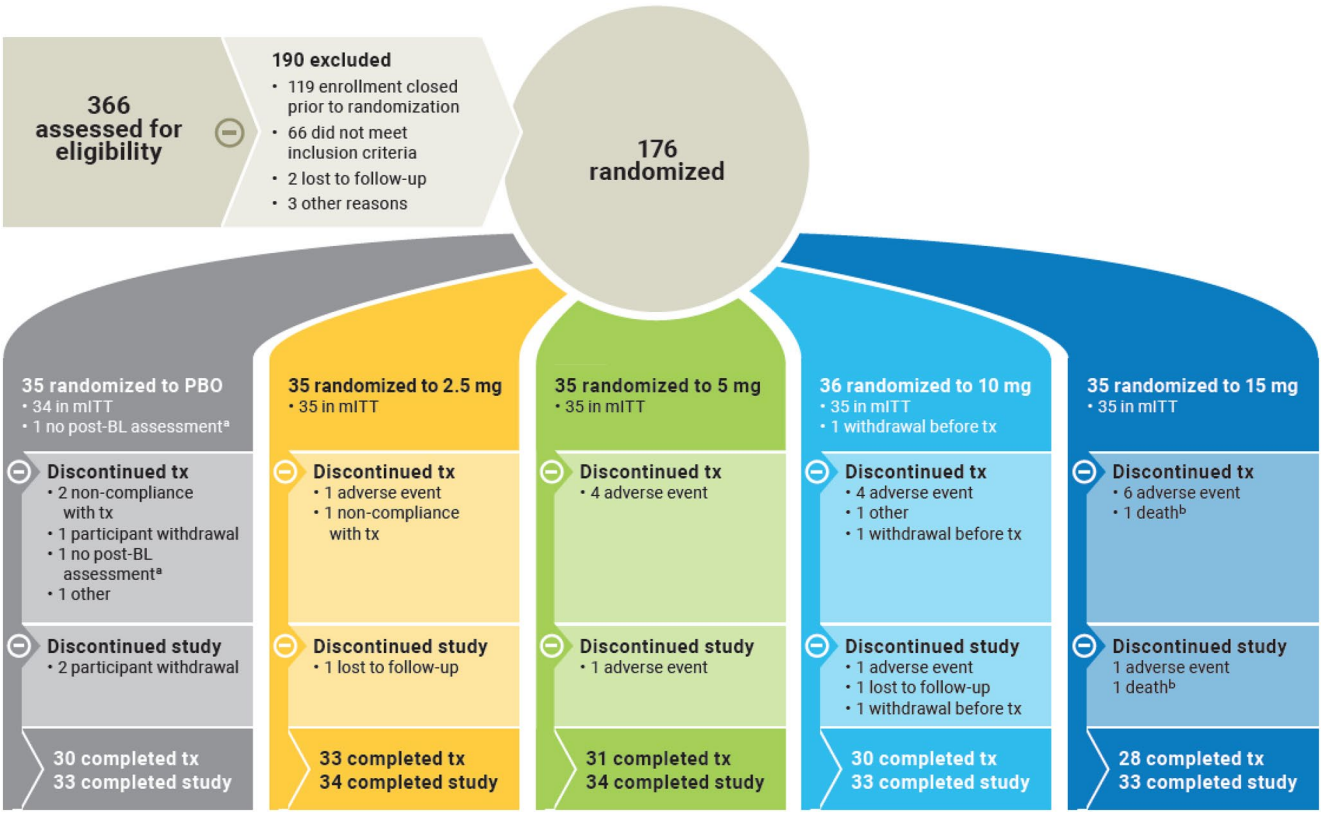

FIGURE 1 | Study flow. [a]No post-baseline assessment within the 9-day post-treatment discontinuation window. [b]The death in the 15 mg group was reported as "head trauma from a fall" and was assessed as not related to study drug. BL, baseline; mITT, modified intent-to-treat population; PBO, placebo; tx, treatment.

used. Prior to performing the model, any assessments taken after treatment discontinuation +9 days were set to missing. The MMRM model used a likelihood-based approach to manage missing data, assuming data were missing completely at random or missing at random.

Least square means, standard errors (SE), and 95% confidence intervals (CI) of the percent change and the difference in the percent change for each treatment group compared with the placebo group were calculated. All tests were two-sided and conducted at a significance level of 0.05. A step-down closed testing procedure was utilized to preserve the family-wise type I error at 0.05 and each dose group was tested versus placebo in the following order: VK2735 15, 10, 5, and 2.5 mg. A nonparametric Wilcoxon rank sum test was also used as a supportive analysis.

Analyses were performed using SAS version 9.4 (SAS Institute Inc.) or higher.

3 | Results

3.1 | Participants

The trial was conducted between August 31, 2023, and February 23, 2024. In total, 176 participants were randomized into the study, with approximately 35 participants randomized to placebo or each active treatment group (Figure 1). The safety population ($N = 175$) excludes one participant in the 10 mg group who did not receive treatment and the mITT population used for efficacy analyses ($N = 174$) excludes that participant and one participant in the placebo group who did not have an evaluable post-baseline assessment.

Overall, 167 of the 176 randomized participants (95%) completed the study. The reasons for early study discontinuation were AEs ($n = 3$), withdrawal by participant ($n = 3$), loss to follow-up ($n = 2$), and death ($n = 1$; Figure 1). A total of 24 of 176 participants (14%) discontinued the treatment early (Figure 1). The most common

TABLE 1 | Demographic and clinical characteristics at baseline for randomized population ($N = 176$).

Characteristic	Placebo ($n = 35$)	2.5 mg ($n = 35$)	5.0 mg ($n = 35$)	10 mg ($n = 36$)	15 mg ($n = 35$)
Age (years)	47.6 (16.36)	49.7 (13.90)	51.8 (14.10)	47.1 (13.40)	51.3 (15.41)
Age category, *n* (%)					
< 65 years	31 (88.6)	27 (77.1)	27 (77.1)	32 (88.9)	27 (77.1)
≥ 65 years	4 (11.4)	8 (22.9)	8 (22.9)	4 (11.1)	8 (22.9)
Sex, *n* (%)					
Female	29 (82.9)	27 (77.1)	23 (65.7)	24 (66.7)	27 (77.1)
Male	6 (17.1)	8 (22.9)	12 (34.3)	12 (33.3)	8 (22.9)
Female reproductive status, *n* (%)					
Childbearing potential	15 (51.7)	13 (48.1)	12 (52.2)	12 (50.0)	11 (40.7)
Postmenopausal for ≥ 12 months	7 (24.1)	10 (37.0)	7 (30.4)	6 (25.0)	7 (25.9)
Surgically sterilized	7 (24.1)	4 (14.8)	4 (17.4)	6 (25.0)	9 (33.3)
Race, *n* (%)					
White	26 (74.3)	28 (80.0)	31 (88.6)	26 (72.2)	28 (80.0)
Black or African American	8 (22.9)	7 (20.0)	2 (5.7)	10 (27.8)	6 (17.1)
American Asian	1 (2.9)	0	2 (5.7)	0	1 (2.9)
Ethnicity, *n* (%)					
Not Hispanic or Latino	28 (80.0)	29 (82.9)	28 (80.0)	30 (83.3)	30 (85.7)
Hispanic or Latino	7 (20.0)	5 (14.3)	7 (20.0)	6 (16.7)	5 (14.3)
Not reported	0	1 (2.9)	0	0	0
Height (cm)	163.49 (9.21)	164.37 (9.41)	165.55 (7.91)	167.24 (9.23)	165.8 (8.56)
Weight (kg)	104.48 (22.18)	103.09 (19.01)	98.32 (13.18)	102.98 (18.27)	101.05 (18.91)
BMI (kg/m^2)	38.88 (6.33)	38.03 (5.56)	35.86 (4.03)	36.62 (4.18)	36.63 (5.25)
Pre-diabetes, *n* (%)[a]	14 (40.0)	21 (60.0)	21 (60.0)	16 (44.4)	16 (45.7)

Note: Values are mean (SD) unless otherwise noted.
[a]Prediabetes defined as fasting plasma glucose 100–125 mg/dL or HbA1c 5.7%–6.4%.

TABLE 2 | Efficacy outcomes at Week 13 ($N = 174$).

	Placebo ($n = 34$)	2.5 mg ($n = 35$)	5.0 mg ($n = 35$)	10 mg ($n = 35$)	15 mg ($n = 35$)
Baseline weight in kg, mean (SD)	105.3 (22.00)	103.1 (19.00)	98.3 (13.18)	103.4 (18.40)	101.0 (18.91)
Percent change in body weight from baseline (primary outcome)					
LS Mean (95% CI)	−1.7 (−3.03, −0.30)	−9.1 (−10.43, −7.76)	−10.9 (−12.25, −9.55)	−12.9 (−14.30, −11.56)	−14.7 (−16.11, −13.38)
LS Mean Difference from PBO (95% CI)	—	−7.43 (−9.34, −5.52)	−9.23 (−11.15, −7.31)	−11.26 (−13.20, −9.33)	−13.08 (−15.01, −11.15)
p value vs. PBO	—	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Change in body weight in kg from baseline					
LS Mean (95% CI)	−1.8 (−3.09, −0.44)	−9.2 (−10.46, −7.86)	−10.7 (−11.97, −9.33)	−13.3 (−14.61, −11.94)	−14.6 (−15.96, −13.30)
LS Mean Difference from PBO (95% CI)	—	−7.40 (−9.26, −5.54)	−8.88 (−10.76, −7.01)	−11.51 (−13.39, −9.63)	−12.86 (−14.74, −10.99)
p value vs. PBO	—	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Weight reduction categories					
Weight reduction of ≥ 5%, *n* (%)	4 (11.5)	28 (80.8)	34 (97.0)	33 (93.8)	35 (100)
Odds ratio vs. PBO (95% CI)	—	26.7 (6.9, 103.2)	148.9 (20.8, > 999.9)	84.6 (15.6, 457.2)	454.1 (23.3, > 999.9)
p value vs. PBO	—	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Weight reduction of ≥ 10%, *n* (%)	1 (3.0)	14 (40.1)	23 (65.1)	25 (70.4)	31 (89.1)
Odds ratio vs. PBO (95% CI)	—	23.6 (2.8, 197.5)	60.2 (7.1, 509.3)	91.5 (10.4, 806.8)	315.5 (30.6, > 999.9)
p value vs. PBO	—	0.0036	0.0002	< 0.0001	< 0.0001
Weight reduction of ≥ 15%, *n* (%)	0	4 (12.8)	4 (11.6)	11 (31.2)	15 (41.5)
Odds ratio vs. PBO (95% CI)	—	11.2 (0.5, 228.2)	9.1 (0.4, 188.6)	35.9 (1.9, 677.1)	52.3 (2.8, 982.7)
p value vs. PBO	—	0.1163	0.1533	0.0169	0.0082

Note: Change and percent change in body weight analyses were conducted using mixed model for repeated measures in the modified intent-to-treat population. The odds ratios, CI, and *p* values were from logistic regression models with treatment as the factor and baseline weight as the covariate. An odds ratio > 1 favors subcutaneous VK2735.
Abbreviations: LS, least squares; PBO, placebo.

reason for early treatment discontinuation was AEs (15/176 participants [8.5%]).

Groups were well matched for baseline characteristics in the randomized population (Table 1), with no significant differences between groups for any parameter. The majority of participants were non-Hispanic, White, and female, and the mean age was approximately 50 years.

3.2 | Efficacy Outcomes

All primary and secondary efficacy endpoints showed significant improvement versus placebo in all treatment groups (Table 2). A dose response was observed for all efficacy measures. Statistically significant differences in the primary outcome of percent change of weight from baseline to Week 13 were observed for all active treatment groups (−9.1% to −14.7%, vs. −1.7% for placebo) in the mITT population (Table 2, Figure 2A). Results from the Wilcoxon rank sum test were consistent with the primary efficacy analysis. In the subset of participants who had post-dose follow-up visits, persistent weight loss was seen at 4- and 7-week follow-up visits (Weeks 16 and 19, respectively), shown in Figure 2B. The intervention in diet and exercise initiated at study start resulted in a significant decrease in weight in the placebo group by Week 13 (1.7%), though the reduction was significantly smaller than the treatment effect (Table 2, Figure 2A).

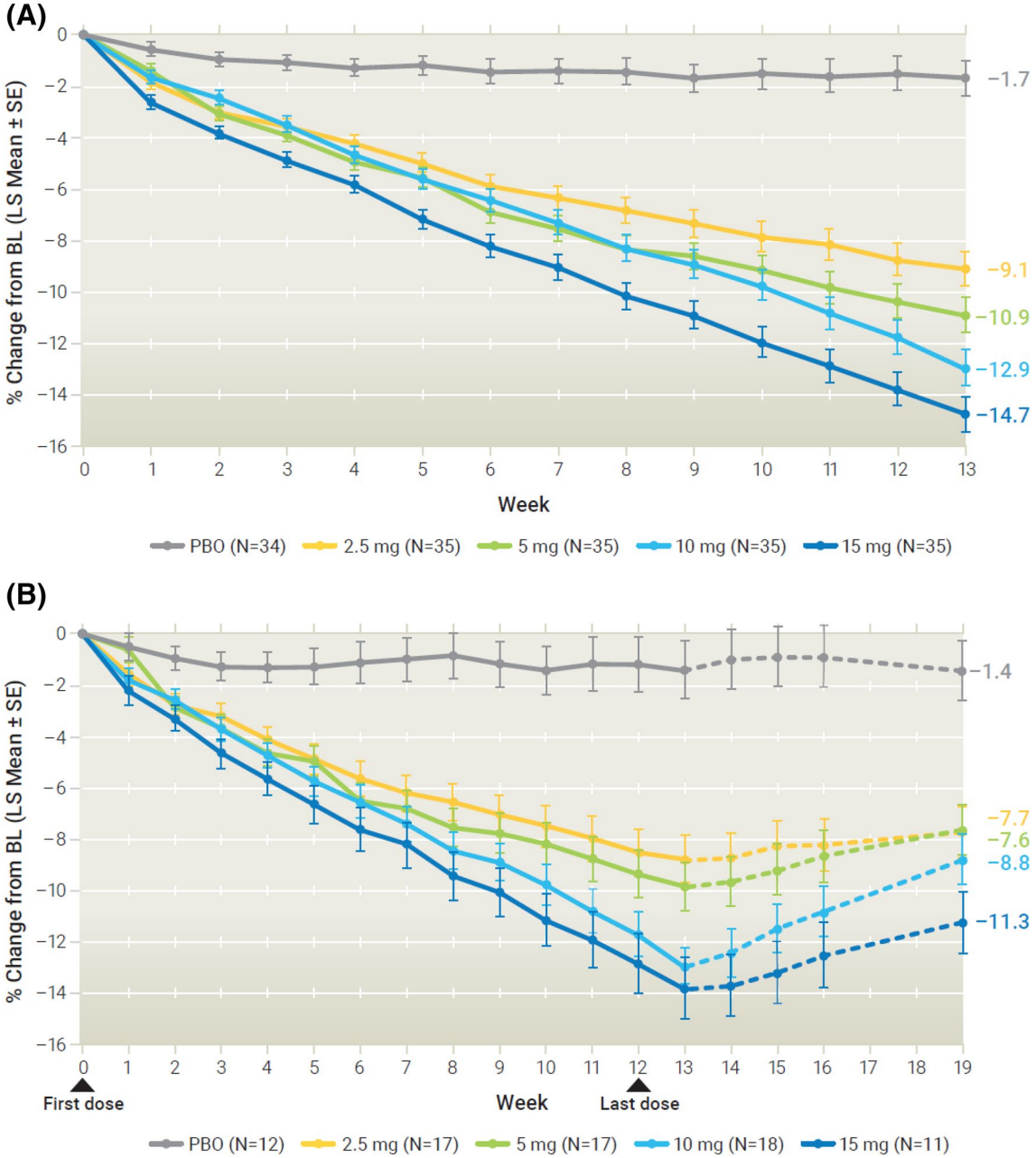

FIGURE 2 | (A) Weight loss by week and dose (13 weeks, $N = 174$). (B) Weight loss by week and dose in subgroup with follow-up visits (19 weeks, $N = 75$). Weight loss over time in the full modified intent-to-treat population (primary outcome, panel A) and the subset of patients with Week 19 follow-up data (panel B). Dashed line indicates follow-up phase of study. BL, baseline; LS, least squares; PBO, placebo.

TABLE 3 | Treatment-emergent adverse events ($N = 175$).

	Placebo ($n = 35$)	2.5 mg ($n = 35$)	5.0 mg ($n = 35$)	10 mg ($n = 35$)	15 mg ($n = 35$)
TEAEs, *n* (%)	24 (69)	25 (71)	31 (89)	30 (86)	32 (91)
Drug-related TEAEs, *n* (%)	16 (46)	21 (60)	27 (77)	26 (74)	30 (86)
TESAEs, *n* (%)[a]	1 (3)	2 (6)	2 (6)	2 (6)	1 (3)
Death, *n* (%)[b]	0	0	0	0	1 (3)
Discontinued treatment early, *n* (%)[c]	5 (14)	2 (6)	4 (11)	5 (14)	7 (20)
TEAE leading to treatment discontinuation	0	1 (3)	4 (11)	4 (11)	7 (20)
Discontinued study early, *n* (%)[c]	2 (6)	1 (3)	1 (3)	2 (6)	2 (6)
TEAE leading to study discontinuation	0	0	1 (3)	1 (3)	1 (3)
Drug-related TEAE leading to study discontinuation	0	0	0	0	1 (3)[d]
TEAEs of special interest, *n* (%)					
Pancreatitis	0	0	0	0	0
Gallbladder associated events[e]	0	1 (3)	0	0	1 (3)
Injection site reactions	3 (9)	2 (6)	5 (14)	5 (14)	4 (11)
Anti-drug Abs,[f] *n*/*N* (%)	—	3/34 (9)	4/34 (12)	8/35 (23)	5/32 (16)
TEAEs in ≥2 participants in any treatment group by preferred term, *n* (%)					
Gastrointestinal disorders	13 (37)	18 (51)	23 (66)	25 (71)	29 (83)
Nausea	7 (20)	9 (26)	16 (46)	13 (37)	22 (63)
Constipation	4 (11)	7 (20)	10 (29)	9 (26)	10 (29)
Diarrhea	3 (9)	11 (31)	6 (17)	7 (20)	4 (11)
Vomiting	0	3 (9)	6 (17)	6 (17)	10 (29)
Gastroesophageal reflux disease	1 (3)	2 (6)	5 (14)	4 (11)	6 (17)
Dry mouth	1 (3)	0	2 (6)	2 (6)	3 (9)
Abdominal pain	1 (3)	1 (3)	2 (6)	1 (3)	2 (6)
Abdominal distension	0	1 (3)	1 (3)	1 (3)	2 (6)
Abdominal pain upper	1 (3)	2 (6)	0	2 (6)	0
Dyspepsia	1 (3)	1 (3)	1 (3)	0	2 (6)
Eructation	0	2 (6)	0	0	3 (9)
Infections and infestations	11 (31)	9 (26)	11 (31)	9 (26)	10 (29)
COVID-19	5 (14)	2 (6)	2 (6)	1 (3)	2 (6)
Upper respiratory tract infection	3 (9)	1 (3)	3 (9)	1 (3)	1 (3)
Sinusitis	1 (3)	1 (3)	1 (3)	2 (6)	2 (6)
Nasopharyngitis	0	2 (6)	2 (6)	1 (3)	1 (3)
Urinary tract infection	0	0	1 (3)	1 (3)	4 (11)
Bronchitis	2 (6)	0	0	0	0
Gastroenteritis	0	0	0	2 (6)	0
Tooth infection	2 (6)	0	0	0	0
General disorders and administration site conditions	5 (14)	8 (23)	9 (26)	10 (29)	12 (34)

(Continues)

TABLE 3 | (Continued)

	Placebo ($n=35$)	2.5 mg ($n=35$)	5.0 mg ($n=35$)	10 mg ($n=35$)	15 mg ($n=35$)
Fatigue	1 (3)	1 (3)	5 (14)	2 (6)	4 (11)
Injection site pain	3 (9)	2 (6)	2 (6)	0	1 (3)
Injection site erythema	0	1 (3)	0	3 (9)	2 (6)
Increased thirst	0	4 (11)	0	1 (3)	1 (3)
Injection site reaction	0	0	1 (3)	2 (6)	0
Pain	0	0	0	2 (6)	1 (3)
Metabolism and nutrition disorders	2 (6)	2 (6)	8 (23)	11 (31)	6 (17)
Decreased appetite	0	2 (6)	5 (14)	9 (26)	6 (17)
Hyperlipidemia	2 (6)	0	0	0	0
Hypokalemia	0	0	0	2 (6)	0
Nervous system disorders	6 (17)	2 (6)	7 (20)	5 (14)	6 (17)
Headache	4 (11)	1 (3)	4 (11)	2 (6)	4 (11)
Dizziness	1 (3)	1 (3)	2 (6)	0	4 (11)
Musculoskeletal and connective tissue disorders	4 (11)	6 (17)	1 (3)	2 (6)	5 (14)
Arthralgia	1 (3)	3 (9)	0	1 (3)	1 (3)
Back pain	0	2 (6)	1 (3)	0	1 (3)
Investigations	2 (6)	2 (6)	7 (20)	1 (3)	5 (14)
C-reactive protein increased	0	0	2 (6)	1 (3)	0
Lipase increased	0	1 (3)	2 (6)	0	0
Respiratory, thoracic, and mediastinal disorders	3 (9)	3 (9)	3 (9)	1 (3)	2 (6)
Nasal congestion	1 (3)	2 (6)	1 (3)	0	0
Vascular disorders	0	2 (6)	2 (6)	1 (3)	3 (9)
Hypotension	0	0	1 (3)	1 (3)	2 (6)
Hypertension	0	2 (6)	0	0	0
Ear and labyrinth disorders	0	1 (3)	5 (14)	1 (3)	0
Vertigo	0	0	3 (9)	1 (3)	0
Endocrine disorders	0	0	0	2 (6)	0
Hyperthyroidism	0	0	0	2 (6)	0

Note: TEAEs were defined as AEs that started on or after the first dose of study drug. AE reported terms were coded using the MedDRA version 26.0. Although a participant may have had 2 or more TEAEs, the participant was counted only once within a SOC and PT. The same participant may have contributed to 2 or more PTs in the same SOC or to 2 different SOCs.

Abbreviations: Abs, antibodies; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

[a]12 SAEs were reported (appendicitis, infected bite, head injury, limb injury, acute kidney injury, urinary incontinence, microcytic anemia, atrial fibrillation, cholecystitis, dehydration, paresthesia, and hypotension) in these 8 participants. Of the 12 SAEs, 10 were considered not related to the study drug and 2 were reported in the same participant as possibly related (atrial fibrillation) and probably related (dehydration).

[b]1 death, due to "head trauma from a fall" with underlying causes of hypertension and hyperlipidemia, was determined to be not related to the study drug. Full details for this patient are included in the online Supporting Information.

[c]Patients could discontinue treatment and remain in the study.

[d]One participant experienced 2 drug-related SAEs (atrial fibrillation and dehydration) leading to withdrawal of study drug. Atrial fibrillation was designated as "possibly related" and dehydration as "probably related" to study drug by the investigator.

[e]Gallbladder associated AEs of special interest were cholecystitis and cholelithiasis.

[f]Anti-VK2735 antibody positive at Week 13.

The majority of patients (81% with 2.5 mg to 100% with 15 mg dose) experienced a ≥5% reduction in body weight at every dose (Table 2). A dose response was seen at the ≥10% weight loss threshold. The highest two doses (10 and 15 mg) resulted in the largest percentage of patients with a ≥15% decrease in body weight.

There was a dose-dependent decrease from baseline for other measures of weight loss, including change in BMI and hip circumference (Table S3).

3.3 | Safety Outcomes

Of the 175 participants in the safety population, 142 (81.1%) experienced at least one TEAE of any type, and 120 of 175 (68.6%) experienced a total of 356 drug-related TEAEs (Table 3). Most drug-related TEAEs were mild or moderate; 71 of 175 participants (40.6%) experienced a maximum severity of grade 1 (mild), 41 (23.4%) grade 2 (moderate), 8 (4.6%) grade 3 (severe), and no participants experienced grade 4 (life-threatening) AEs. The most common study drug-related TEAEs were nausea (64/175 participants [36.6%]), constipation (37/175 [21.1%]), and vomiting (22/175 [12.6%]).

One (0.6%) participant died during the study. Cause of death was reported as "head trauma from a fall" with underlying causes of hypertension and hyperlipidemia, and it was assessed as not related to the study drug. Additional patient details can be found in the online Supporting Information.

In total, 16 of 175 participants (9.1%) experienced at least one TEAE leading to withdrawal of the study drug. The most common TEAEs experienced by these participants were nausea (five participants), vomiting (four participants), diarrhea (two participants), and headache (two participants). No other AEs were experienced by more than one participant who discontinued treatment due to TEAEs.

Study and treatment discontinuation rates due to TEAEs are shown in Table 3. A total of 8 of 175 participants (4.6%) experienced a total of 12 TESAEs. The 12 TESAEs reported were

TABLE 4 | Drug-related gastrointestinal AEs by severity (≥ 2 participants in any group and any severity), *n* (%).

	Placebo (*n* = 35)	2.5 mg (*n* = 35)	5.0 mg (*n* = 35)	10 mg (*n* = 35)	15 mg (*n* = 35)
Any gastrointestinal disorder					
Mild—Grade 1	8 (23)	8 (23)	14 (40)	13 (37)	16 (46)
Moderate—Grade 2	4 (11)	7 (20)	9 (26)	7 (20)	10 (29)
Severe—Grade 3	0	1 (3)	0	1 (3)	3 (9)
Life-threatening—Grade 4	0	0	0	0	0
Death—Grade 5	0	0	0	0	0
Nausea					
Mild	7 (20)	5 (14)	11 (31)	8 (23)	15 (43)
Moderate	0	2 (6)	5 (14)	4 (11)	7 (20)
Constipation					
Mild	2 (6)	3 (9)	8 (23)	6 (17)	9 (26)
Moderate	2 (6)	2 (6)	1 (3)	2 (6)	1 (3)
Vomiting					
Mild	0	2 (6)	4 (11)	5 (14)	5 (14)
Moderate	0	0	2 (6)	0	3 (9)
Diarrhea					
Mild	2 (6)	4 (11)	5 (14)	2 (6)	1 (3)
Moderate	0	2 (6)	1 (3)	0	3 (9)
Gastroesophageal reflux disease					
Mild	0	1 (3)	1 (3)	2 (6)	4 (11)
Moderate	1 (3)	1 (3)	3 (9)	2 (6)	2 (6)
Dry mouth, mild	1 (3)	0	2 (6)	2 (6)	2 (6)
Abdominal distension, mild	0	1 (3)	1 (3)	1 (3)	2 (6)
Abdominal pain, mild	1 (3)	0	2 (6)	0	1 (3)
Dyspepsia, moderate	1 (3)	0	1 (3)	0	2 (6)
Eructation, mild	0	2 (6)	0	0	3 (9)
Abdominal pain upper, mild	1 (3)	2 (6)	0	1 (3)	0

appendicitis, infected bite, head injury, limb injury, acute kidney injury, urinary incontinence, microcytic anemia, atrial fibrillation, cholecystitis, dehydration, paranesthesia, and hypotension. Ten of the twelve TESAEs were considered unrelated to the study drug by investigators. One participant in the 5.0 mg dose group experienced two drug-related TESAEs, atrial fibrillation (possibly related) and dehydration (probably related), which led to study discontinuation.

A total of 27 TEAEs of special interest, injection site reaction being the most common, were experienced by 21 of 175 participants (12.0%; Table 3). At Week 13, anti-drug antibodies were detected in between 9% (2.5 mg group) and 23% (10 mg group) of participants in any treatment group (Table 3).

3.4 | Gastrointestinal (GI) TEAEs (Most Common TEAEs)

The majority of GI-related TEAEs were mild or moderate in severity and no grade 4 or 5 TEAEs were observed (Table 4). Nausea was the most common GI TEAE and had the highest severity (Tables 3 and 4). Nausea was highest in the first week in the 15 mg dose group; this group had a 5.0 mg starting dose, rather than the 2.5 mg starting dose in all other treatment groups (Figure 3 and Figure S1). GI AEs were generally observed early in the study and subsided over time (Figure 3). No dose-dependent increase in GI TEAEs was observed after initial dosing (Figure 3).

3.5 | Change in Cardiometabolic Measures

In general, cardiometabolic parameters improved in VK2735 treatment groups (Table 5). Of the 74 participants who had prediabetes at baseline, 58 (78%) shifted to normoglycemic at Week 13 in the active treatment groups and none shifted from prediabetes to diabetes. Lipid markers generally declined over the 13-week study in the active treatment group ($N = 141$). Only total cholesterol had a p value less than 0.05 versus placebo ($p = 0.0396$) in this time frame.

4 | Discussion

The high affinity of the GLP-1/GIP receptor dual agonist VK2735 for both receptors results in a peptide intended to elicit a favorable response on cardiometabolic endpoints of importance in the setting of obesity. Weekly subcutaneous dosing with VK2735 led to significant weight loss after 13 weeks of treatment. In the lowest dose group, this was a 9.1% change from baseline, and in the highest dose group, a 14.7% decrease was observed. At Week 12 of a weekly dosing regimen, participants treated with semaglutide were reported to have an approximately 6% decrease from baseline in body weight [23], and those treated with tirzepatide had an approximately 8% decrease from baseline in body weight [20].

The majority of participants (66%) experienced a greater than 10% weight loss from baseline with subcutaneous VK2735

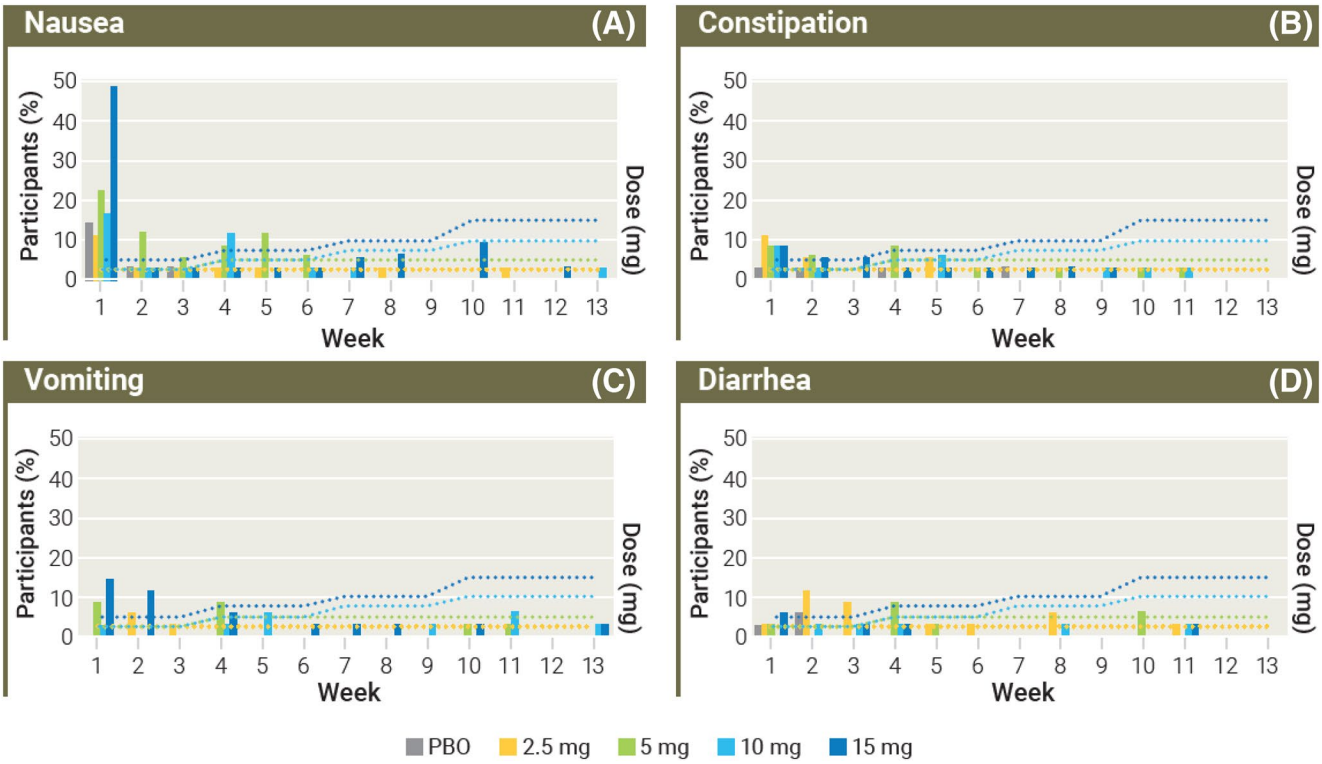

FIGURE 3 | Duration of GI TEAEs ($N = 175$). The most common GI TEAEs are shown in the four panels: (A) nausea, (B) constipation, (C) vomiting, and (D) diarrhea. The percentage of participants at each week who reported the specific GI AE for that panel is shown as a bar. The dose at each week for each group is shown as a dashed line reflecting the dose titration schedule shown in Figure S1. Most groups started with 2.5 mg dose, with the 15 mg dose group starting at 5.0 mg. GI, gastrointestinal; PBO, placebo; TEAE, treatment-emergent adverse event.

TABLE 5 | Change from baseline in key cardiometabolic measures at Week 13 ($N = 176$).

	Placebo ($n = 35$)	2.5 mg ($n = 35$)	5.0 mg ($n = 35$)	10 mg ($n = 36$)	15 mg ($n = 35$)
hsCRP, mg/L[a]					
BL, mean (SD)	8.00 (11.807)	4.25 (4.693)	7.22 (11.534)	5.03 (5.800)	7.08 (10.133)
BL, median	4.50	3.50	4.00	3.40	3.70
Change from BL, median	0.20	0.10	−0.30	−0.10	−0.75
Systolic blood pressure, mmHg					
BL, mean (SD)	125.10 (13.963)	126.20 (14.754)	128.60 (15.253)	122.64 (13.764)	123.36 (14.531)
Change from BL, LS Mean (SE)	**−4.20 (1.993)**	**−6.87 (1.906)**	**−6.71 (1.931)**	**−7.04 (1.936)**	**−10.97 (2.000)**
Diastolic blood pressure, mmHg					
BL, mean (SD)	80.93 (9.169)	81.56 (9.491)	82.91 (7.904)	79.00 (9.420)	78.39 (7.332)
Change from BL, LS Mean (SE)	−1.68 (1.286)	**−3.27 (1.229)**	**−4.34 (1.246)**	**−2.37 (1.247)**	**−5.16 (1.290)**
Heart rate, bpm					
BL, mean (SD)	74.2 (11.01)	69.9 (10.46)	70.2 (10.45)	71.7 (8.53)	69.3 (9.94)
Change from BL, mean (SD)	1.4 (12.15)	3.3 (11.94)	6.1 (9.33)	9.3 (8.51)	6.9 (8.43)
Glycemic status					
Glucose, mg/dL					
BL, mean (SD)	99.37 (9.932)	100.31 (9.320)	99.77 (9.478)	97.97 (8.687)	99.06 (7.685)
Change from BL, LS Mean (SE)	−0.37 (1.475)	**−10.66 (1.439)**	**−10.23 (1.424)**	**−9.46 (1.424)**	**−10.85 (1.456)**
Hemoglobin A1c, %					
BL, mean (SD)	5.49 (0.361)	5.51 (0.360)	5.43 (0.399)	5.50 (0.357)	5.50 (0.312)
Week 13, mean (SD)	5.53 (0.387)	5.22 (0.297)	5.17 (0.405)	5.25 (0.372)	5.12 (0.332)
Change from BL, LS Mean (SE)	0.03 (0.041)	**−0.29 (0.040)**	**−0.27 (0.040)**	**−0.27 (0.039)**	**−0.36 (0.040)**
Shift in diabetes status[b]					
Prediabetes at baseline, *n*	14	21	21	16	16
Shift to normoglycemic, *n* (%)	4 (28.6)	**17 (81.0)**	**16 (76.2)**	10 (62.5)	**15 (93.8)**
Shift to diabetes, *n* (%)	1 (7.1)	0	0	0	0

Note: Bold number indicates $p < 0.05$ for change from baseline value or versus placebo for shift in diabetes status.
Abbreviations: BL, baseline; hsCRP, high-sensitivity C-reactive protein; LS, least squares.
[a]Safety population, 10 mg $n = 35$; no statistical analyses performed.
[b]Categories of glycemic control defined by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) are: normoglycemic = FPG < 100 mg/dL and HbA1c < 5.7%, prediabetes = FPG 100–125 mg/dL or HbA1c 5.7%–6.4%, and diabetes = FPG > 125 mg/dL or HbA1c > 6.4%.

treatment. Despite the brevity of the trial, a significant benefit was seen in glucose status for many patients. Of those who began the study as having prediabetes, 78% were normoglycemic at Week 13. Similar improvements were observed among individuals who met the criteria for metabolic syndrome at baseline.

The majority of TEAEs were mild or moderate and short-lived despite continued treatment. While the TEAE profile was similar to semaglutide and tirzepatide in that GI TEAEs were most common [20, 23], few long-term GI TEAEs were observed. Given that the 5 mg dose had a higher GI TEAE rate than the 10 mg dose, there does not seem to be a dose-dependent increase in GI TEAEs if a 2.5 mg starting dose is used at the beginning of the titration phase. The clear benefit of starting below 5.0 mg and titrating up has informed the phase 3 trial design to further improve tolerability. Despite being a phase 2 dose-finding study with an abbreviated titration schedule, the TEAE rates of 69% to 91% and SAE rates of 3% to 6% reported with VK2735 treatment are similar to those reported in the phase 3 trials for weekly semaglutide (90% AE rate, 10% SAE rate) [23] and tirzepatide (79%–82% AE rate, 5%–7% SAE rate) [20]. Maximal therapeutic levels were likely not yet achieved in this limited duration study.

Use of dual GIP/GLP-1 receptor agonists in combination with behavioral modification (e.g., reduced calorie diet and exercise) facilitates clinically meaningful weight loss that may prevent or attenuate the progression of obesity-related chronic comorbidities [24–27]. Long-term benefit of these treatments requires persistence with the treatment, which is more easily achieved if the treatment has a favorable tolerability profile [28, 29]. Alternative dosing options may help improve persistence with GLP-1/GIP receptor agonists, including the possibility of monthly subcutaneous maintenance dosing and daily oral options. The data obtained during this study have informed the phase 3 study design, which will further elucidate the potential of VK2735 as a treatment for obesity.

This is a phase 2 study and was therefore limited in size and duration. As a dose-finding study designed to inform the VK2735 phase 3 program, some aspects of the VENTURE study, such as titration schedule and dosing, will be changed to optimize tolerability in future studies. It was not powered to determine statistical significance for differences between treatment groups for most parameters.

5 | Conclusion

In addition to demonstrating clinically meaningful weight loss, VK2735 had a favorable tolerability profile in this short-term study. The efficacy and safety data collected here will inform the phase 3 study design for treatment of obesity with VK2735.

Author Contributions

H.B., S.J., S.S., and **B.L.:** full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. **S.J., S.S.,** and **B.L.:** collection, management, analysis, and interpretation of the data. **S.J.:** statistical analysis. **B.L.:** supervision. All authors: conduct of the study; review and approval of the manuscript; reading and approving the final manuscript for submission.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data will be available upon request. Data can be accessed upon request by researchers who submit a methodologically sound proposal and agree to a Data Access Agreement.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.