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VENTURE: Impact of VK2735, a Dual Incretin Agonist, on Predicted Cardiovascular Disease Risk

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INTRODUCTION

- In 2022, approximately 2.5 billion adults were overweight, of which 890 million were living with obesity[1]
- Obesity is a chronic, systemic disease that contributes to the development of multiple chronic comorbid conditions, including cardiovascular disease (CVD)
- CVD remains the world's leading cause of death and economic burden, with atherosclerotic cardiovascular disease (ASCVD) alone accounting for an estimated $680 billion in direct healthcare costs globally[2]
- Studies have demonstrated the cardioprotective role of glucagon-like peptide 1 (GLP-1) receptor agonists, including reduced cardiovascular mortality, lower rates of myocardial infarction, and lower rates of stroke[3]
- GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonists likely confer cardiovascular benefit through multiple pathways (e.g., body weight and adiposity reduction, reduced systemic inflammation)[4]
- VK2735 is a long-acting dual GLP-1/ GIP receptor agonist that has demonstrated significant weight reduction and improvements in cardiometabolic parameters in a Phase 2 trial of the subcutaneous (SC) formulation[5]

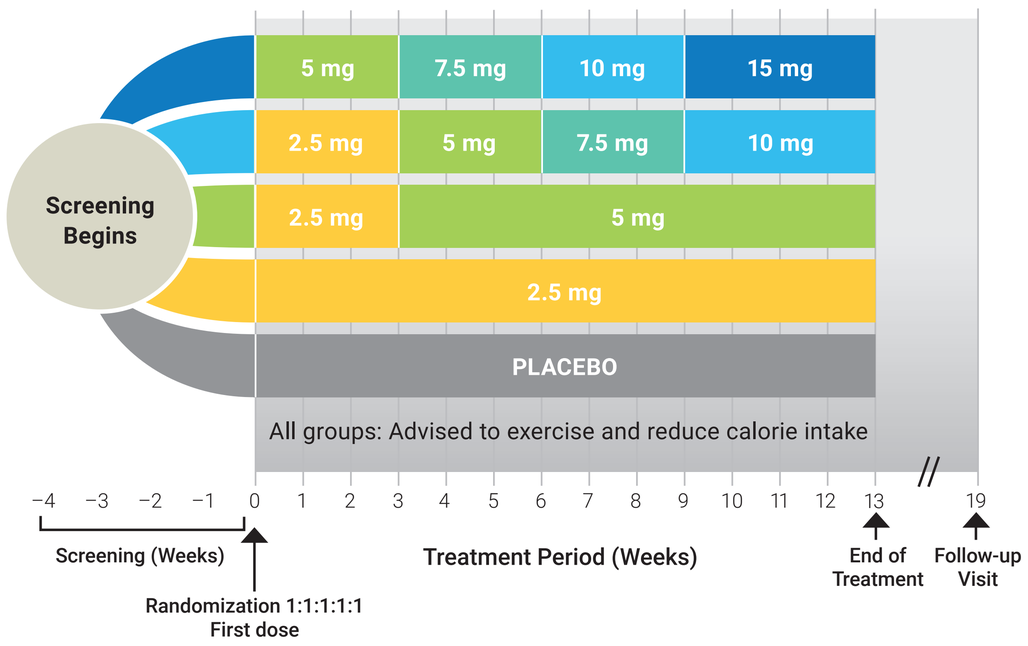
OBJECTIVES

- This analysis examines the impact of weekly SC VK2735 on 10-year predicted risk of CVD, ASCVD, and heart failure following 13 weeks of treatment

METHODS

- Phase 2, randomized, double-blind, placebo-controlled study intended to evaluate the safety, tolerability, pharmacokinetics, and weight loss efficacy of SC VK2735 after 13 weeks of treatment (NCT06068946)
- Adults with BMI ≥30 kg/m^2 or ≥27 kg/m^2 and ≥1 weight-related comorbid condition received once-weekly SC VK2735 or matched placebo for 13 weeks
- The primary VENTURE endpoint was percent change in body weight from baseline to week 13 versus placebo
- These post hoc analyses show the predicted 10-year CVD, ASCVD, and heart failure risk[6] at baseline and week 13 for the subset of patients between 30 and 79 years of age without preexisting cardiac disorders

Study design



Baseline demographics for VENTURE CVD analysis subset

mITT N=174 ⊖ age <30 or >79 years old n=17
Age-adjusted subset n=157 ⊖ participants w/ any cardiac disorder n=14
CVD risk subset n=143

Characteristic	Placebo (n=27)	All VK2735 (n=116)
Age, years, mean (SD)	51.9 (12.2)	51.8 (12.1)
Female, n (%)	22 (81.5)	84 (72.4)
Race, n (%)		
White	21 (77.8)	95 (81.9)
Asian	0 (0)	2 (1.7)
Black or African American	6 (22.2)	19 (16.4)
Ethnicity, n (%)		
Not Hispanic or Latino	22 (81.5)	94 (81.0)
Weight, kg, mean (SD)	107.1 (21.9)	100.3 (17.1)
BMI, kg/m^2, mean (SD)	39.6 (6.6)	36.5 (4.8)
BMI category, n (%)		
27 to <30	1 (3.7)	8 (6.9)
Class 1 Obesity, 30 to <35	6 (22.2)	40 (34.5)
Class 2 Obesity, 35 to <40	7 (25.9)	41 (35.3)
Class 3 Obesity, ≥40	13 (48.2)	27 (23.3)
Pre-diabetes,[a] n (%)	14 (51.9)	68 (58.6)
MetS,[b] n/N (%)	16 (59.3)	67 (57.8)
Current Smoker, Yes (%)	2 (7.4)	15 (12.9)
Current Statin user to lower cholesterol, Yes (%)	5 (18.5)	30 (25.9)
Current hypertension medication user, Yes (%)	12 (44.4)	40 (34.5)

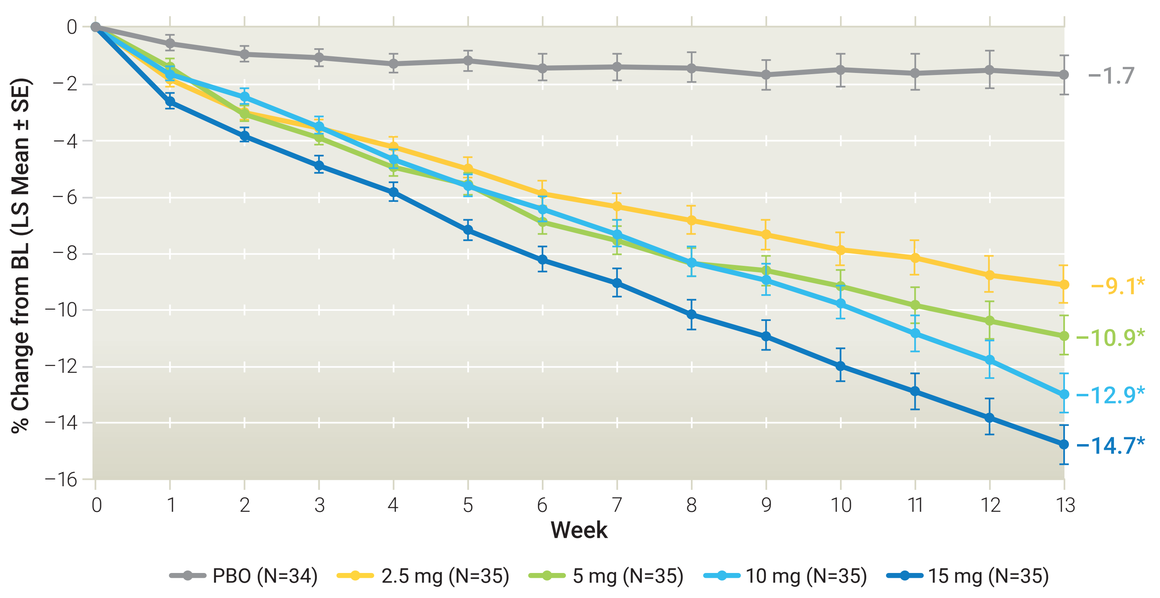
[a]Pre-diabetes defined as FPG 100 – 125 mg/dL or HbA1c 5.7 – 6.4%.
[b]Participants who met MetS criteria at baseline. MetS criteria: ≥3 of 5 criteria: abdominal obesity (waist >40 in [men], >35 in [women]), high BP, elevated fasting glucose, high triglycerides, or low HDL.

Abbreviations: BL, baseline; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; MetS, metabolic syndrome; mITT, modified intent-to-treat.

WEEKLY SC VK2735 TREATMENT WAS ASSOCIATED WITH LOWER 10-YEAR PREDICTED RISK OF CVD, ASCVD, AND HEART FAILURE COMPARED TO PLACEBO

Weight loss by week 13

- Participants in every VK2735 treatment group had significant weight loss from baseline within 13 weeks
- No weight loss plateau was observed at week 13



*P < .0001.
Abbreviations: BL, baseline; PBO, placebo.

Predicted 10-year CV risk

Endpoint	LS mean difference (% change from baseline)	Difference (95% CI)	*P* value
10-year CVD		−4.14 (−17.22, 8.94)	.532
10-year ASCVD		−6.67 (−19.44, 6.09)	.303
10-year HF		−16.21 (−27.37, −5.06)	.005

−30 −20 −10 0 10
◀ Favors VK2735 Favors Placebo ▶

LS mean treatment difference in 10-year CV risk scores at week 13 (total active vs placebo). Placebo n=20, VK2735 n=90.

MMRM model; dependent variable is % change of risk from baseline. Independent variables include treatment group, visit, visit × treatment group interaction, and baseline risk. Participants younger than 30, older than 79, or with any pre-existing CVD were excluded.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures.

Analysis of treatment effect on CM parameters

Parameter	Better if	Mean difference	SMD (95% CI)
HbA1c, %	▼ Lower	−0.32	−1.49 (−2.01, −0.97)
BMI, kg/m²	▼ Lower	−3.52	−2.32 (−2.90, −1.75)
Total cholesterol, mg/dL	▼ Lower	−8.03	−0.26 (−0.75, 0.22)
SBP, mmHg	▼ Lower	−2.40	−0.20 (−0.69, 0.28)
eGFR, mL/min/1.73m²	▲ Higher	−2.28	−0.28 (−0.77, 0.20)
Triglycerides, mg/dL	▼ Lower	−11.90	−0.22 (−0.70, 0.27)
LDL, mg/dL	▼ Lower	−3.98	−0.14 (−0.63, 0.34)

−3 −2 −1 0 1
◀ VK2735 compared with PBO change ▶

SMD = (mean VK2735 - mean placebo) / pooled standard deviation; shown with ~ 95% CI. Placebo n=20, VK2735 n=90.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

CONCLUSIONS

- Following a 13-week treatment period, average 10-year predicted CVD, ASCVD, and HR risk was lower in the weekly SC VK2735 treatment group compared to both baseline and placebo in adults with obesity or overweight with ≥1 weight-related comorbidity
- The 78-week Phase 3 VANQUISH-1 (NCT07104500) and VANQUISH-2 (NCT07104383) studies are currently ongoing and will further inform the efficacy and safety of VK2735 in adults with obesity or overweight

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DISCLOSURES

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