

RESEARCH MONOGRAPH . COMPOUND PROFILE

VK-2735

A 39-amino-acid acylated incretin peptide developed by Viking Therapeutics as a dual agonist of the glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide receptors, demonstrating robust weight reduction and glycemic improvement in Phase 1 and Phase 2 clinical trials and advancing through Phase 3 registration studies for chronic weight management in adults with obesity.

DOCUMENT	KDC-MN-1408
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Dual GLP-1/GIP receptor agonist acylated peptide for obesity and metabolic disease

RESEARCH USE ONLY

ABSTRACT

VK-2735 is a synthetic, acylated 39-amino-acid peptide dual agonist of the glucagon-like peptide 1 receptor (GLP-1R) and the glucose-dependent insulintropic polypeptide receptor (GIPR), developed by Viking Therapeutics, Inc. (San Diego, California) as a candidate therapeutic for chronic weight management and metabolic disease. The compound binds both incretin receptors with high affinity (GLP-1R IC₅₀ 188 nM; GIPR IC₅₀ 325 nM) and activates the canonical Gs-coupled adenylate cyclase/cAMP signaling cascades that underlie glucose-dependent insulin secretion, appetite suppression, delayed gastric emptying, and enhanced lipid metabolism [1]. The dual-agonist mechanism places VK-2735 in the same pharmacological class as tirzepatide (Eli Lilly), the first dual GLP-1/GIP receptor agonist approved for the treatment of obesity and type 2 diabetes, and distinguishes it from the selective GLP-1 receptor agonists semaglutide and liraglutide by the addition of GIP receptor-mediated activity on adipose tissue, pancreatic beta cells, and central appetite circuits. VK-2735 was selected from an internally developed series of dual-agonist peptides characterized at ObesityWeek 2021 in diet-induced obese mouse models, in which the Viking compounds produced weight loss, glucose normalization, insulin sensitization, and hepatic fat reduction that exceeded the effects of equimolar semaglutide and were broadly comparable to tirzepatide [2]. The compound has been formulated for both subcutaneous injection (weekly dosing) and oral tablet administration (daily dosing), a dual-formulation strategy that is unusual in the incretin peptide class and that, if successful in registration, would provide the first oral dual GLP-1/GIP receptor agonist approved for human use. In

the Phase 1 subcutaneous trial (NCT05203237), single and multiple ascending doses in healthy adults with elevated body mass index demonstrated a plasma elimination half-life of approximately 170 to 250 hours, a time to maximum plasma concentration of approximately 75 to 90 hours, predictable dose-proportional pharmacokinetics, and mean placebo-adjusted body weight reductions of up to 6.0 percent after 28 days of weekly dosing, with 98 percent of adverse events classified as mild or moderate [3, 4]. In the Phase 2 VENTURE trial (NCT06068946), 176 adults with obesity or overweight with at least one weight-related comorbidity were randomized to weekly subcutaneous VK-2735 at 2.5, 5.0, 10, or 15 mg or placebo for 13 weeks; the primary endpoint of percent change in body weight from baseline was met at all dose levels, with least-squares mean reductions of 9.1, 10.9, 12.9, and 14.7 percent, respectively, versus 1.7 percent on placebo (all $p < 0.0001$), with 100 percent of participants in the 15 mg arm achieving at least 5 percent weight loss and 89.1 percent achieving at least 10 percent weight loss [1]. Weight loss trajectories showed no plateau at 13 weeks. Of 74 participants with prediabetes at baseline, 78 percent shifted to normoglycemic status across the active treatment arms with no new cases of diabetes. The Phase 1 oral tablet trial demonstrated dose-dependent weight loss of up to 5.3 percent from baseline at 40 mg daily over 28 days, with a gastrointestinal adverse-event profile that was notably mild relative to the subcutaneous formulation and included no vomiting events [5]. The Phase 2 VENTURE-Oral trial in 280 adults with obesity randomized across six dose arms (15, 30, 60, 90, 120 mg daily, and a maintenance cohort) or placebo for 13 weeks demonstrated up to 12.2 percent mean weight loss at the 120 mg dose, with up to 97 percent of participants achieving at least 5 percent weight loss [6]. The principal adverse events across

all formulations and trials are gastrointestinal: nausea, vomiting, constipation, and diarrhea, consistent with the incretin agonist class and generally mild to moderate in severity, with decreasing frequency upon continued dosing. VK-2735 is currently in Phase 3 evaluation in two large registration trials (VANQUISH-1, approximately 4,650 participants, and VANQUISH-2, approximately 1,000 participants with type 2 diabetes) evaluating subcutaneous weekly dosing for 78 weeks with a 52-week extension, and Viking has announced plans to advance the oral formulation to Phase 3 in the third quarter of 2026 [7, 8]. The compound is not approved by any regulatory authority. It is available only through clinical trial enrollment or as a research-grade preparation from chemical suppliers. This monograph reviews the chemistry and peptide structure, the dual-receptor pharmacology in molecular detail, the comprehensive pharmacokinetic record across subcutaneous and oral formulations, the preclinical and clinical evidence base, reconstitution and handling, stack-interaction considerations, the adverse-event and safety signal, and a comparative assessment of five alternative obesity pharmacotherapies against VK-2735 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Development code: VK2735 (Viking Therapeutics). The development code is the canonical identifier in all published clinical and preclinical literature; no international nonproprietary name has been assigned as of the date of this monograph.

Alternate designations: VK-2735, Viking 2735. The compound is referenced without a hyphen in the majority of Viking Therapeutics corporate communications and clinical trial registrations (VK2735) and with a hyphen in some secondary literature (VK-2735); both forms refer to the same molecule.

Chemical Abstracts Service registry number: Not publicly assigned. The compound is a proprietary peptide with an undisclosed primary amino acid sequence; no CAS registry number has been deposited in the public Chemical Abstracts database as of May 2026.

UNII (Unique Ingredient Identifier): Not publicly assigned as of May 2026.

ClinicalTrials.gov identifiers: NCT05203237 (Phase 1, subcutaneous), NCT06068946 (Phase 2 VENTURE, subcutaneous), VENTURE-Oral (Phase 2, oral tablet), NCT07104500 (Phase 3 VANQUISH-1, subcutaneous), VANQUISH-2 (Phase 3, subcutaneous, type 2 diabetes population).

1.2 Structural class and chemistry

VK-2735 is an acylated peptide of 39 amino acid residues with an estimated molecular weight of approximately 4,000 daltons [9]. The compound belongs to the incretin mimetic structural class, a group of synthetic peptides engineered to activate one or more of the three principal metabolic hormone receptors: the glucagon-like peptide 1 receptor (GLP-1R), the glucose-dependent insulintropic polypeptide receptor (GIPR), and the glucagon receptor (GCGR). VK-2735 is a dual agonist of GLP-1R and GIPR; it does not have characterized activity at the glucagon receptor.

The peptide backbone is derived from the native GLP-1 and GIP sequences with amino acid substitutions engineered to confer dual-receptor binding, resistance to dipeptidyl peptidase-4 (DPP-4) proteolytic degradation, and prolonged plasma half-

life. The acyl side chain, a common modification in the long-acting incretin peptide class (shared with semaglutide, tirzepatide, and liraglutide), enables non-covalent binding to serum albumin, which serves as a circulating depot that extends the plasma elimination half-life from minutes (the native incretin hormones) to days (the therapeutic peptides) [10].

Molecular formula: Not publicly disclosed. The proprietary sequence has not been deposited in public databases.

Molecular weight: Approximately 4,000 daltons (estimated from the 39-amino-acid acylated peptide designation) [9].

Physical properties: The compound is supplied as a lyophilized powder for reconstitution (subcutaneous formulation) and as an oral tablet (oral formulation). Solubility characteristics of the free peptide and the formulated tablet excipient composition have not been publicly disclosed.

Stereochemistry: The peptide comprises L-amino acids in the standard ribosomal configuration; non-natural amino acid substitutions, if present, have not been disclosed.

1.3 Synthesis

The synthesis of VK-2735 has not been described in the public literature. Based on the structural class (39-amino-acid acylated peptide), the compound is expected to be produced by solid-phase peptide synthesis using fluorenylmethyloxycarbonyl (Fmoc) chemistry on a polymeric resin support, followed by on-resin or post-cleavage acylation with a fatty acid linker, global side-chain deprotection, resin cleavage, and purification by reverse-phase high-performance liquid chromatography [10]. The acylation step, which attaches the albumin-binding fatty acid moiety, is a critical determinant of the pharmacokinetic half-life extension and is performed at a specific lysine residue in the peptide chain. Industrial-scale production of peptides in this class typically employs convergent fragment condensation or recombinant expression followed by chemical acylation, depending on the sequence length and the scale requirements. Viking Therapeutics has not disclosed the manufacturing site, the synthetic route, or the scale-up strategy for VK-2735.

2. Abstract

VK-2735 is a dual agonist of the glucagon-like peptide 1 receptor (GLP-1R) and the glucose-dependent insulintropic polypeptide receptor (GIPR), a 39-amino-acid acylated peptide developed by Viking Therapeutics for chronic weight management in adults with obesity or overweight and for the treatment of associated metabolic comorbidities including type 2 diabetes, nonalcoholic steatohepatitis, and dyslipidemia [1, 2].

The compound activates both GLP-1R and GIPR at pharmacologically relevant concentrations (GLP-1R IC₅₀ 188 nM; GIPR IC₅₀ 325 nM) and produces the canonical incretin-mediated physiological effects: glucose-dependent potentiation of insulin secretion from pancreatic beta cells, suppression of inappropriately elevated glucagon secretion, delayed gastric emptying, central appetite suppression through hypothalamic and brainstem circuits, and enhancement of peripheral lipid metabolism and adipose tissue function [1, 11]. The dual-agonist mechanism, in which GIP receptor activation amplifies and complements GLP-1 receptor activation, distinguishes VK-2735 from the selective GLP-1R agonists semaglutide (Wegovy, Ozempic) and liraglutide (Saxenda, Victoza) and places it in the same pharmacological class as tirzepatide (Mounjaro, Zepbound), the first approved dual GLP-1/GIP receptor agonist [12].

The clinical development program has advanced through Phase 1 (subcutaneous and oral formulations), Phase 2 (subcutaneous VENTURE trial and oral VENTURE-Oral trial), and into Phase 3 (subcutaneous VANQUISH-1 and VANQUISH-2 trials). The subcutaneous Phase 2 VENTURE trial (Bays et al. 2026) demonstrated 14.7 percent mean body weight reduction at the 15 mg weekly dose over 13 weeks versus 1.7 percent on placebo, with 100 percent of participants in the highest dose arm achieving at least 5 percent weight loss and 89.1 percent achieving at least 10 percent [1]. Weight loss trajectories were progressive with no plateau at 13 weeks. Glycemic improvements were substantial: 78 percent of participants with baseline prediabetes shifted to normoglycemic status, with no new cases of diabetes [1]. The oral Phase 2 VENTURE-Oral trial demonstrated 12.2 percent mean weight loss at the 120 mg daily dose over 13 weeks versus 1.3 percent on placebo, with up to 97 percent achieving at least 5 percent weight loss [6].

Pharmacokinetics of the subcutaneous formulation are characterized by a long plasma elimination half-life of 170 to 250 hours (approximately 7 to 10 days), a time to maximum concentration of 75 to 90 hours, and dose-proportional exposure, consistent with weekly dosing and potentially supporting biweekly or monthly dosing regimens [3, 4].

The adverse-event profile is dominated by gastrointestinal events (nausea, vomiting, constipation, diarrhea), consistent with the incretin agonist class. In the subcutaneous VENTURE trial, 95 percent of gastrointestinal adverse events were mild or moderate, and symptom frequency decreased with continued dosing [1]. The oral formulation demonstrated a notably mild gastrointestinal profile in Phase 1, with 14 percent nausea incidence and no vomiting [5]. In the Phase 2 oral trial, higher doses (90 to 120 mg) produced nausea rates of approximately 58 percent (99 percent mild or moderate), with a 28 percent overall discontinuation rate that included gastrointestinal-related withdrawals [6].

VK-2735 is not approved by any regulatory authority. Phase 3 results from the VANQUISH-1 trial (approximately 4,650 participants, 78-week treatment) and VANQUISH-2 trial (approximately 1,000 participants with type 2 diabetes) are expected in the second half of 2026 and 2027, respectively [7, 8]. Viking has announced plans to advance the oral formulation to Phase 3 in the third quarter of 2026 [8]. This monograph documents the peptide chemistry, dual-receptor pharmacology, comprehensive pharmacokinetics, preclinical and clinical evidence, sourcing and handling, stack interactions, adverse-event signal, and comparative assessment of five alternative incretin-based obesity pharmacotherapies.

3. Discovery and Development History

3.1 Origin

VK-2735 was developed internally at Viking Therapeutics, Inc., a clinical-stage biopharmaceutical company headquartered in San Diego, California. Viking was founded in 2012 and has focused its research pipeline on metabolic and endocrine disorders, including programs in thyroid receptor beta agonism (VK2809 for nonalcoholic steatohepatitis) and incretin receptor agonism for obesity and type 2 diabetes.

The VK-2735 program originated from a medicinal chemistry effort to develop best-in-class dual GLP-1/GIP receptor agonist peptides. Viking presented preclinical data from a series of internally developed dual-agonist compounds at ObesityWeek 2021, demonstrating that the Viking series produced superior weight loss, glucose normalization, and hepatic fat reduction compared to equimolar semaglutide (a selective GLP-1R agonist) in diet-induced obese mouse models, and comparable or numerically superior effects relative to tirzepatide on liver fat endpoints [2]. VK-2735 was selected from this series as the lead clinical candidate on the basis of receptor affinity, pharmacokinetic profile, and tolerability in preclinical toxicology studies.

3.2 Phase 1 development (subcutaneous)

Viking initiated the Phase 1 clinical trial (NCT05203237) of subcutaneous VK-2735 in January 2022. The study was a randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy adults with elevated body mass index. Results were announced in March 2023 [3]. The SAD portion established the pharmacokinetic profile (half-life 170 to 250 hours, T_{max} 75 to 90 hours). The MAD portion evaluated weekly subcutaneous dosing for 28 days across five dose-escalation cohorts (0.5 mg, 1.5 mg, 1.5/3/5/5 mg, 3/5/5/7.5 mg, and 5/5/7.5/10 mg) in 31 VK-2735-treated subjects and 10 placebo-treated subjects. The two highest-dose cohorts produced statistically significant placebo-adjusted weight loss of 5.6 percent (p=0.0003) and 6.0 percent (p=0.0002), respectively, after only 28

days [3]. No hypoglycemia was observed despite robust incretin pathway activation. Additional data presented at ObesityWeek 2023 confirmed that weight loss differences were maintained or improved at 21 days post-treatment (Day 43) [4].

3.3 Phase 1 development (oral)

Viking initiated a Phase 1 MAD trial of an oral tablet formulation of VK-2735 in the first quarter of 2023. Results announced in March 2024 demonstrated safety, tolerability, and dose-dependent weight loss at daily doses of 2.5, 5, 10, 20, and 40 mg over 28 days [5]. The 40 mg dose produced 5.3 percent mean weight loss from baseline (3.3 percent placebo-adjusted, $p=0.0006$), with 57 percent of subjects achieving at least 5 percent weight loss. The gastrointestinal adverse-event profile was notably mild: 14 percent nausea (all mild), no vomiting, and no clinically meaningful differences from placebo [5]. The oral formulation was described as achieving systemic absorption without food restrictions, a feature that distinguishes it from the oral semaglutide formulation (Rybelsus), which requires fasting and water-volume restrictions.

3.4 Phase 2 VENTURE trial (subcutaneous)

Viking initiated the Phase 2 VENTURE trial (NCT06068946) in September 2023. The trial enrolled 176 adults with obesity (BMI at least 30 kg/m²) or overweight (BMI at least 27 kg/m²) with at least one weight-related comorbidity at 20 United States sites. Participants were randomized 1:1:1:1:1 to weekly subcutaneous VK-2735 at 2.5, 5.0, 10, or 15 mg or placebo for 13 weeks. Top-line results were announced in February 2024, and the full results were published in the peer-reviewed journal *Obesity* by Bays et al. in January 2026 [1]. The trial achieved its primary endpoint at all dose levels. The study period was August 31, 2023, to February 23, 2024. Detailed results are presented in Section 7 (Clinical Evidence Base).

3.5 Phase 2 VENTURE-Oral trial

Viking initiated the Phase 2 VENTURE-Oral trial in 2024, enrolling 280 adults with obesity or overweight randomized across six VK-2735 dosing arms (15, 30, 60, 90, 120 mg daily, and a maintenance cohort of 90 mg down-titrated to 30 mg) or placebo for 13 weeks. Top-line results announced in August 2025 demonstrated up to 12.2 percent mean weight loss at the 120 mg dose [6]. Detailed results are presented in Section 7.

3.6 Phase 3 VANQUISH program

Viking initiated the Phase 3 VANQUISH-1 trial, enrolling approximately 4,650 adults with obesity or overweight, evaluating weekly subcutaneous VK-2735 versus placebo for 78 weeks with a 52-week extension period, with the primary endpoint of percent change in body weight from baseline. The trial is designed to evaluate weekly, biweekly, and monthly dosing regimens. Enrollment in VANQUISH-1 was completed in December 2025 [7]. The Phase 3 VANQUISH-2 trial, enrolling approximately 1,000 adults with type 2 diabetes and obesity or overweight, was fully enrolled in March 2026 [8]. Results from VANQUISH-2 are expected in the third quarter of 2026. Viking has announced plans to advance the oral formulation to Phase 3 in the third quarter of 2026 [8].

4. Mechanism of Action

VK-2735 is a dual incretin receptor agonist. Its principal molecular activities are agonism at the glucagon-like peptide 1 receptor and agonism at the glucose-dependent insulintropic polypeptide receptor. These activities operate through overlapping and complementary downstream signaling pathways to produce the observed effects on body weight, appetite, glucose homeostasis, lipid metabolism, and inflammation.

4.1 GLP-1 receptor agonism

The GLP-1 receptor (GLP-1R) is a class B (secretin family) G-protein-coupled receptor expressed at high density on pancreatic beta cells, on gastric parietal and smooth muscle cells, on vagal afferent neurons, in the hypothalamic arcuate nucleus and area postrema, in the nucleus tractus solitarius of the brainstem, and at lower density in the heart, kidney, and immune cells [11, 12]. Native GLP-1 is a 30- or 31-amino-acid incretin hormone secreted by intestinal L cells in response to nutrient ingestion; it has a plasma half-life of approximately 2 minutes owing to rapid degradation by dipeptidyl peptidase-4 (DPP-4) and renal clearance.

VK-2735 binds the GLP-1R with an IC₅₀ of 188 nM in competitive binding assays [1]. Upon binding, the receptor couples to the stimulatory G- α -s subunit of the heterotrimeric G protein, activating adenylate cyclase and increasing intracellular cyclic adenosine monophosphate (cAMP). Elevated cAMP activates protein kinase A (PKA) and exchange protein activated by cAMP 2 (EPAC2), which in turn modulate ion channel activity, elevate cytosolic calcium concentrations, and promote exocytosis of insulin-containing secretory granules from pancreatic beta cells in a glucose-dependent manner [11, 13]. The glucose dependence of the insulin secretory response is a critical pharmacological feature: incretin-mediated insulin release requires ambient glucose concentrations above a threshold (approximately 4 to 5 mmol/L), which substantially reduces the risk of hypoglycemia relative to sulfonylureas and exogenous insulin.

The central nervous system effects of GLP-1R activation are the principal mediators of the appetite-suppressive and weight-reducing activity. GLP-1R activation on neurons in the hypothalamic arcuate nucleus suppresses neuropeptide Y (NPY) and

agouti-related peptide (AgRP) orexigenic signaling and potentiates pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) anorexigenic signaling [14]. GLP-1R activation in the brainstem nucleus tractus solitarius and area postrema produces nausea and satiety signals that further reduce food intake. The gastrointestinal effect of delayed gastric emptying, mediated through vagal afferent GLP-1R activation, prolongs postprandial satiety and reduces nutrient absorption rate.

4.2 GIP receptor agonism

The GIP receptor (GIPR) is a class B G-protein-coupled receptor expressed at high density on pancreatic beta cells, on adipocytes, on osteoblasts, and in the central nervous system including the hypothalamus [15, 16]. Native GIP is a 42-amino-acid incretin hormone secreted by intestinal K cells in response to nutrient ingestion, with a plasma half-life of approximately 5 to 7 minutes owing to DPP-4 degradation.

VK-2735 binds the GIPR with an IC₅₀ of 325 nM [1]. GIPR signaling proceeds through the same Gs-coupled adenylate cyclase/cAMP pathway as GLP-1R, activating PKA and EPAC2 in beta cells to potentiate glucose-dependent insulin secretion. However, GIPR activation produces distinct effects in non-beta-cell tissues that complement and amplify the GLP-1R activity [15, 16].

In adipose tissue, GIPR activation promotes adipogenesis, lipid uptake, and triglyceride storage in subcutaneous adipose depots while reducing ectopic lipid deposition in liver and muscle, an effect that may improve insulin sensitivity by redirecting lipid from metabolically harmful visceral and hepatic depots to metabolically favorable subcutaneous depots [16]. In the central nervous system, GIPR activation modulates appetite and energy expenditure through circuits that are partially distinct from GLP-1R circuits, providing an additive or synergistic anorectic signal [15].

The differential G-protein coupling of the two receptors may contribute to the enhanced efficacy of dual agonism. In murine pancreatic beta cells, GLP-1 activates both G-alpha-s and G-alpha-q, whereas GIP selectively activates G-alpha-s; the composite signaling from dual-receptor activation therefore produces a broader intracellular signal repertoire than either receptor alone [13, 15].

4.3 Composite pharmacology and the dual-agonist advantage

The rationale for dual GLP-1/GIP receptor agonism is supported by both preclinical and clinical evidence. In diet-induced obese mouse models, the Viking series of dual-agonist compounds produced greater weight loss and metabolic improvement than equimolar semaglutide (GLP-1R-selective), supporting the thesis that addition of GIP receptor activity improves upon the effects of GLP-1 receptor activation alone [2]. The clinical evidence from the VENTURE trial demonstrates weight loss of up to 14.7 percent at 13 weeks, a rate that compares favorably with the early trajectories reported for tirzepatide (the approved dual GLP-1/GIP agonist) and that substantially exceeds the early weight-loss trajectory of semaglutide at comparable time points [1, 12, 17].

The composite pharmacology of VK-2735 at the doses used in the VENTURE trial produces near-maximal incretin-mediated effects: robust appetite suppression, delayed gastric emptying, glucose-dependent insulin potentiation, glucagon suppression, and improved adipose tissue lipid handling. The dose-response relationship across the 2.5 to 15 mg weekly subcutaneous range demonstrates a monotonic increase in weight loss without plateau, suggesting that higher doses or longer treatment durations may produce additional weight reduction, a hypothesis that the 78-week VANQUISH trials are designed to test [7, 8].

4.4 Selectivity

VK-2735 is designed as a selective GLP-1R/GIPR dual agonist. No characterized activity at the glucagon receptor has been reported, distinguishing the compound from the triple-agonist class (retatrutide, which activates GLP-1R, GIPR, and GCGR) and from the GLP-1/glucagon dual-agonist class (survodutide, which activates GLP-1R and GCGR without GIP receptor activity) [18, 19]. The absence of glucagon receptor activity eliminates the potential liabilities of glucagon-mediated hepatic glucose output and thermogenesis but also forgoes the potential benefits of glucagon receptor-mediated hepatic fat reduction and energy expenditure that are being pursued in the triple-agonist programs.

5. Pharmacokinetics and Routes of Administration

5.1 Subcutaneous formulation: absorption

Following single subcutaneous doses, VK-2735 demonstrates a time to maximum plasma concentration (T_{max}) of approximately 75 to 90 hours (3 to 4 days) and dose-proportional increases in maximum plasma concentration (C_{max}) and area under the curve (AUC) across the studied dose range [3, 4]. The prolonged T_{max} reflects the combination of the subcutaneous depot effect and the albumin-binding acyl chain, which retains the peptide in the circulation through reversible non-covalent association with serum albumin.

5.2 Subcutaneous formulation: distribution

Distribution parameters have not been publicly disclosed in full. Based on the structural class (acylated albumin-binding peptide), the volume of distribution is expected to be small relative to body weight, consistent with the peptide remaining predominantly in the plasma and interstitial fluid compartments bound to albumin. Serum albumin binding is the principal determinant of the large apparent volume of distribution and the long elimination half-life, as the albumin-peptide complex is protected from renal filtration and from proteolytic degradation by DPP-4 and neutral endopeptidases.

5.3 Subcutaneous formulation: metabolism and elimination

The plasma elimination half-life of subcutaneous VK-2735 is approximately 170 to 250 hours (7 to 10 days), supporting weekly dosing and potentially biweekly or monthly dosing regimens [3, 4]. The VANQUISH-1 Phase 3 trial is evaluating weekly, biweekly, and monthly dosing schedules [7]. The extended half-life is attributable to the albumin-binding acyl chain, which protects the peptide from DPP-4 degradation and from renal filtration in the same manner as semaglutide (half-life approximately 168 hours) and tirzepatide (half-life approximately 120 hours) [10, 12].

Metabolic degradation pathways have not been disclosed. Based on the peptide class, elimination is expected to proceed through proteolytic degradation to component amino acids with renal excretion of the fatty acid moiety and degradation products, with no involvement of cytochrome P450 enzymes in the primary elimination pathway.

5.4 Oral formulation: pharmacokinetics

The oral tablet formulation of VK-2735 achieves systemic bioavailability through a mechanism that has not been publicly disclosed. Unlike oral semaglutide (Rybelsus), which requires the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) and imposes strict fasting and water-volume restrictions, the VK-2735 oral formulation has been described as achieving absorption without food restrictions [5, 9]. Specific pharmacokinetic parameters (T_{max}, C_{max}, AUC, absolute bioavailability, half-life) for the oral formulation have not been publicly disclosed in detail. The Phase 2 oral trial evaluated daily dosing at 15 to 120 mg, suggesting that oral bioavailability is substantially lower than subcutaneous bioavailability (the subcutaneous efficacious dose being 2.5 to 15 mg weekly versus oral doses of 15 to 120 mg daily), a relationship consistent with the known low oral bioavailability of peptide therapeutics [6].

5.5 Routes of administration

Two routes are in clinical development: subcutaneous injection (weekly, biweekly, or monthly dosing under evaluation) and oral tablet (daily dosing). The subcutaneous formulation is supplied as a solution in a single-dose prefilled syringe or autoinjector for self-administration. The oral formulation is supplied as a tablet. Intravenous, intramuscular, and other parenteral routes have not been reported.

5.6 Special populations

Pharmacokinetic characterization in special populations (renal impairment, hepatic impairment, pediatric, geriatric, pregnancy, lactation) has not been disclosed. The Phase 2 VENTURE trial excluded participants with diabetes, with estimated glomerular filtration rate below 30 mL/min/1.73 m², and with significant hepatic disease [1]. The Phase 3 VANQUISH-2 trial includes participants with type 2 diabetes. Pediatric studies have not been announced.

6. Preclinical Pharmacology

6.1 Diet-induced obese mouse models

Viking presented preclinical data at ObesityWeek 2021 from a series of dual GLP-1/GIP receptor agonist compounds evaluated in diet-induced obese (DIO) C57BL/6 mice [2]. Animals were treated with vehicle, semaglutide (GLP-1R-selective agonist), tirzepatide (dual GLP-1/GIP agonist), or the Viking series compounds at equivalent doses for the same treatment duration.

The Viking compounds, including VK-2735, produced weight loss that exceeded equimolar semaglutide at the same dose for the same treatment period, supporting the hypothesis that addition of GIP receptor activity improves upon GLP-1 receptor activation alone. The weight-loss effects were broadly comparable to those of tirzepatide. Fasting glucose and insulin levels were normalized in the Viking compound-treated animals, and glucose tolerance testing demonstrated improved glucose clearance relative to vehicle-treated and semaglutide-treated animals [2].

6.2 Hepatic fat reduction

Reductions in hepatic triglyceride content were generally numerically larger among animals treated with the Viking compounds relative to tirzepatide-treated animals, suggesting a potential advantage in the treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis [2]. This finding, combined with the established effects of GLP-1R agonism on hepatic steatosis and the GIP receptor-mediated redirection of lipid from visceral and hepatic depots to subcutaneous adipose tissue, provides preclinical support for the investigation of VK-2735 in NASH-related indications.

6.3 Preclinical toxicology

Formal preclinical toxicology data have not been publicly disclosed. The advancement of VK-2735 to Phase 1 clinical trials indicates completion of the required good laboratory practice (GLP) toxicology package, which for peptide therapeutics in this class typically includes single-dose and repeat-dose toxicity studies in rodent

and non-rodent species, genotoxicity assessment, reproductive and developmental toxicity studies, and safety pharmacology evaluations of cardiovascular, respiratory, and central nervous system endpoints.

7. Clinical Evidence Base

7.1 Phase 1 subcutaneous trial (NCT05203237)

The Phase 1 trial enrolled 41 subjects in the MAD portion: 31 receiving VK-2735 and 10 receiving placebo. The trial evaluated five dose-escalation cohorts: 0.5 mg weekly (n=6), 1.5 mg weekly (n=6), 1.5/3/5/5 mg escalating weekly (n=7), 3/5/5/7.5 mg escalating weekly (n=6), and 5/5/7.5/10 mg escalating weekly (n=6) [3].

Mean weight loss from baseline at Day 28 ranged from 2.5 percent (0.5 mg) to 7.8 percent (5/5/7.5/10 mg). Placebo-adjusted weight loss ranged from 0.7 percent (0.5 mg) to 6.0 percent (5/5/7.5/10 mg, $p=0.0002$). The two highest-dose cohorts achieved statistically significant placebo-adjusted weight loss: 5.6 percent (3/5/5/7.5 mg, $p=0.0003$) and 6.0 percent (5/5/7.5/10 mg, $p=0.0002$). Weight loss was maintained or improved at Day 43 (21 days post-treatment), consistent with the long half-life [3, 4].

Safety: 98 percent of adverse events were mild or moderate. Nausea occurred in 58 percent of VK-2735-treated subjects (89 percent mild, 11 percent moderate) and in 50 percent of placebo subjects. Vomiting occurred in 19 percent (6/31) of VK-2735 subjects. No hypoglycemia was observed. One serious adverse event (acute cholelithiasis in a subject with gallstone history) was reported. No subjects discontinued due to gastrointestinal adverse events [3].

7.2 Phase 2 VENTURE trial (subcutaneous)

The VENTURE trial (NCT06068946; Bays et al. 2026) enrolled 176 adults (mean BMI approximately 37 kg/m², mean age approximately 49 years, approximately 74 percent female) at 20 United States sites [1].

Primary endpoint (percent change in body weight, Week 13, mITT): Placebo: -1.7 percent. VK-2735 2.5 mg: -9.1 percent. VK-2735 5.0 mg: -10.9 percent. VK-2735 10 mg: -12.9 percent. VK-2735 15 mg: -14.7 percent. All active arms achieved $p<0.0001$ versus placebo [1].

Absolute weight loss: Placebo: -1.8 kg. VK-2735 2.5 mg: -9.2 kg. VK-2735 5.0 mg: -10.7 kg. VK-2735 10 mg: -13.3 kg. VK-2735 15 mg: -14.6 kg [1].

Responder rates (at least 5 percent weight loss): Placebo: 11.5 percent. VK-2735 2.5 mg: 80.8 percent. VK-2735 5.0 mg: 97.0 percent. VK-2735 10 mg: 93.8 percent. VK-2735 15 mg: 100 percent. Odds ratios versus placebo ranged from 26.7 (2.5 mg) to 454.1 (15 mg) [1].

Responder rates (at least 10 percent weight loss): Placebo: 3.0 percent. VK-2735 2.5 mg: 40.1 percent. VK-2735 5.0 mg: 65.1 percent. VK-2735 10 mg: 70.4 percent. VK-2735 15 mg: 89.1 percent [1].

Responder rates (at least 15 percent weight loss, exploratory): Placebo: 0 percent. VK-2735 10 mg: 31.2 percent. VK-2735 15 mg: 41.5 percent [1].

Glycemic outcomes: Fasting glucose reductions ranged from -9.46 to -10.85 mg/dL across active arms versus -0.37 mg/dL on placebo (all $p < 0.05$). HbA1c reductions ranged from -0.27 to -0.36 percentage points versus +0.03 on placebo (all $p < 0.05$). Of 74 participants with prediabetes at baseline, 78 percent shifted to normoglycemic status in the active arms, and no participants progressed to diabetes [1].

Cardiovascular parameters: Systolic blood pressure reductions ranged from -6.71 to -10.97 mmHg across active arms versus -4.20 mmHg on placebo. Heart rate increases were dose-dependent, ranging from +3.3 to +9.3 beats per minute across active arms versus +1.4 on placebo [1]. Lipid markers generally declined, with total cholesterol reaching statistical significance versus placebo ($p = 0.0396$).

Inflammatory markers: High-sensitivity C-reactive protein (hsCRP) showed dose-dependent reductions in active arms, with median changes ranging from +0.10 to -0.75 mg/L versus +0.20 on placebo [1].

Post-treatment follow-up: Weight loss persisted at 4-week and 7-week post-dose follow-up visits (Weeks 16 and 19) in the evaluable subset ($N = 75$), consistent with the long elimination half-life [1].

7.3 Phase 1 oral tablet trial

The oral Phase 1 trial enrolled 47 subjects: 37 receiving VK-2735 at daily doses of 2.5, 5, 10, 20, or 40 mg and 10 receiving placebo for 28 days [5]. Mean weight loss from baseline at the 40 mg dose was 5.3 percent (3.3 percent placebo-adjusted, $p = 0.0006$). The proportion achieving at least 5 percent weight loss was 57 percent at 40 mg ($p = 0.015$) versus 0 percent on placebo. All adverse events were mild (76 per-

cent) or moderate. Nausea occurred in 14 percent of VK-2735 subjects (all mild); no vomiting was reported. Diarrhea occurred in 3 percent of VK-2735 subjects versus 20 percent of placebo [5].

7.4 Phase 2 VENTURE-Oral trial

The VENTURE-Oral trial enrolled 280 adults with obesity or overweight across seven arms (placebo and six active dosing arms: 15, 30, 60, 90, 120 mg daily, and a maintenance cohort of 90 mg down-titrated to 30 mg daily) for 13 weeks [6].

Weight loss (percent change from baseline): Placebo: -1.3 percent. VK-2735 15 mg: -2.3 percent. VK-2735 30 mg: -7.0 percent. VK-2735 60 mg: -8.7 percent. VK-2735 90 mg: -11.1 percent. VK-2735 120 mg: -12.2 percent. Maintenance cohort (90/30 mg): -9.2 percent [6].

Responder rates: Up to 97 percent of VK-2735 recipients achieved at least 5 percent weight loss versus 10 percent for placebo. Up to 80 percent achieved at least 10 percent weight loss versus 5 percent for placebo [6].

Weight loss was progressive across all doses above 15 mg, with no plateau at 13 weeks and statistically significant differences from baseline and placebo starting at Week 1 for all doses above 15 mg [6].

7.5 Phase 3 VANQUISH program

The VANQUISH-1 trial is evaluating subcutaneous VK-2735 at weekly, biweekly, and monthly dosing regimens versus placebo for 78 weeks with a 52-week extension in approximately 4,650 adults with obesity or overweight [7]. Enrollment was completed in December 2025. The VANQUISH-2 trial is evaluating weekly subcutaneous VK-2735 versus placebo for 78 weeks in approximately 1,000 adults with type 2 diabetes and obesity or overweight [8]. Enrollment was completed in March 2026. The primary endpoint for both trials is percent change in body weight from baseline at 78 weeks; secondary and exploratory endpoints include percentage of participants achieving weight-loss thresholds (at least 5, 10, 15, and 20 percent) and changes following transition to maintenance dosing.

8. Sourcing and Quality Verification

VK-2735 is an investigational compound that is not approved for any indication by any regulatory authority. The compound is available only through enrollment in Viking Therapeutics clinical trials or as a research-grade preparation from select chemical and peptide research suppliers.

Research-grade VK-2735 is offered by peptide synthesis companies (AbMole BioScience, MedChemExpress, and others) as a lyophilized powder at research-grade purity (typically greater than 95 percent by HPLC). Pricing, lot sizes, and availability vary by supplier and are subject to change. The proprietary nature of the amino acid sequence means that research-grade preparations are synthesized based on publicly available structural information (39-amino-acid acylated peptide) and may not be identical to the clinical-trial material produced by Viking Therapeutics; investigators should treat research-grade VK-2735 as a best-effort approximation of the clinical compound and should not assume clinical-grade identity or purity without independent analytical verification.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Mass spectrometry confirmation of molecular weight (expected approximately 4,000 daltons for the intact acylated peptide)
- Amino acid analysis or peptide sequencing (Edman degradation or tandem mass spectrometry) to confirm sequence identity against any published partial sequence data
- Endotoxin testing (limulus amebocyte lysate assay) for lots intended for in vivo research
- Residual solvent and trifluoroacetic acid or acetate counterion quantification

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) can provide independent confirmation of vendor certificates of analysis. Given the proprietary nature of the compound and the absence of a pharmacopoeial reference

standard, independent verification is particularly important for any investigation where dose-response precision is relevant.

9. Reconstitution and Handling

The subcutaneous clinical formulation of VK-2735 is supplied as a solution in a single-dose prefilled syringe; reconstitution is not required for the clinical material. The oral formulation is supplied as a tablet; no preparation is required.

For research-grade VK-2735 supplied as a lyophilized powder, reconstitution follows standard peptide handling practices:

Reconstitution: Dissolve the lyophilized powder in sterile water for injection, bacteriostatic water (0.9 percent benzyl alcohol), or normal saline (0.9 percent sodium chloride) to the desired concentration. Gentle swirling or rotation is preferred over vortexing to avoid peptide aggregation and foam formation. If higher concentrations are required and the peptide is not freely soluble in aqueous vehicles, a small volume of dimethyl sulfoxide (DMSO, typically not exceeding 10 percent of the final volume) may be used as a co-solvent, followed by dilution with aqueous vehicle.

Storage of reconstituted solution: Refrigerate at 2 to 8 degrees Celsius. Use within 14 to 30 days for bacteriostatic water preparations or within 24 hours for sterile water preparations. Protect from light as a precautionary measure. Avoid repeated freeze-thaw cycles; aliquoting into single-use volumes at the time of reconstitution is recommended.

Storage of lyophilized powder: Store at -20 degrees Celsius for long-term storage or at 2 to 8 degrees Celsius for short-term storage (up to 3 months). Protect from moisture and light. Desiccant should be maintained in the storage container.

Stability: Acylated peptides in this class are generally stable under refrigerated conditions for weeks to months when reconstituted in aqueous vehicles at neutral pH. Acidic conditions (pH below 4) may promote deamidation and aggregation; strongly alkaline conditions (pH above 9) may promote racemization. The optimal pH for storage is approximately 6 to 7.5.

10. Stack Interaction Considerations

VK-2735 is a peptide that is degraded by proteolysis rather than by cytochrome P450-mediated hepatic metabolism. Consequently, the drug-drug interaction profile is expected to differ substantially from that of small-molecule therapeutics. Investigators and clinicians should consider the following interactions:

Delayed gastric emptying effects: VK-2735, like all GLP-1R agonists, delays gastric emptying. This can reduce the rate and potentially the extent of absorption of co-administered oral medications, including oral contraceptives, antibiotics, immunosuppressants, and thyroid hormone replacement. Medications with narrow therapeutic indices that depend on consistent oral absorption (warfarin, levothyroxine, cyclosporine, oral contraceptives) should be monitored during VK-2735 initiation and dose titration. The FDA labeling for tirzepatide and semaglutide includes specific guidance on oral contraceptive interactions [12].

Insulin and sulfonylureas: Co-administration of VK-2735 with insulin or sulfonylureas increases the risk of hypoglycemia. Dose reduction of the insulin or sulfonylurea may be required when initiating VK-2735 in patients with type 2 diabetes receiving these agents. The Phase 1 trial of VK-2735 did not report hypoglycemia in otherwise healthy subjects, consistent with the glucose-dependent mechanism of incretin-mediated insulin secretion [3].

Other GLP-1R agonists: Concurrent use with another GLP-1R agonist (semaglutide, liraglutide, dulaglutide, exenatide) is pharmacologically redundant and not recommended. Combination with a GLP-1R/GIPR agonist (tirzepatide) is similarly redundant and not studied.

GIP receptor agonists: No standalone GIP receptor agonists are currently approved for clinical use; however, investigators using research-grade GIP agonists in combination with VK-2735 should consider additive GIPR-mediated effects on pancreatic beta cells and adipose tissue.

Glucagon receptor agonists or antagonists: VK-2735 does not have characterized activity at the glucagon receptor, but combination with glucagon receptor agonists (as in the triple-agonist class, retatrutide) would produce additive metabolic effects and should be approached with caution in research contexts.

QT-prolonging agents: The incretin peptide class has not been associated with QT prolongation in dedicated thorough QT studies. No specific QT interaction signal has been reported for VK-2735.

Medications affected by weight loss: Substantial weight loss (greater than 10 percent) can alter the pharmacokinetics and pharmacodynamics of co-administered medications through changes in volume of distribution, protein binding, and hepatic and renal clearance. Investigators should consider dose re-evaluation of concomitant medications in subjects experiencing substantial weight loss during VK-2735 treatment.

Cholecystolithiasis risk: One serious adverse event of acute choledocholithiasis was reported in the Phase 1 trial in a subject with pre-existing gallstone disease [3]. Rapid weight loss is an established risk factor for gallstone formation and biliary complications. Co-administration with other agents that promote rapid weight loss or that alter bile acid metabolism (ursodeoxycholic acid, fibrates) should be considered in the context of this risk.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events across all formulations and trials are gastrointestinal, consistent with the incretin agonist class:

Subcutaneous VENTURE trial (VK-2735-treated participants, n=140) [1]:

- Nausea: 36.6 percent overall across active arms (20 percent at 2.5 mg to 63 percent at 15 mg); 68 percent of nausea events classified as mild, 32 percent moderate, 0 percent severe
- Constipation: 21.1 percent overall (20 percent at 2.5 mg to 29 percent at 15 mg)
- Vomiting: 12.6 percent overall (9 percent at 2.5 mg to 29 percent at 15 mg); 0 percent vomiting in placebo
- Diarrhea: dose-variable (11 to 31 percent)
- Any gastrointestinal disorder: 51 to 83 percent across active arms versus 37 percent on placebo
- Injection site reactions: 12 percent

Gastrointestinal adverse events were generally observed early in treatment, with decreasing frequency upon continued dosing. Ninety-five percent of gastrointestinal-specific adverse events were mild or moderate [1].

Oral VENTURE-Oral trial (VK-2735-treated participants) [6]:

- Nausea: 58 percent (99 percent mild or moderate)
- Vomiting: 26 percent
- Constipation: 20 to 43 percent (dose-dependent)
- Diarrhea: 5 to 25 percent (dose-dependent)
- Ninety-eight percent of drug-related adverse events were mild or moderate; 99 percent of gastrointestinal events were mild or moderate
- Weekly nausea and vomiting rates did not exceed 5 percent after Week 3

Phase 1 oral trial [5]:

- Nausea: 14 percent (all mild)
- Vomiting: 0 percent
- Diarrhea: 3 percent
- No clinically meaningful differences from placebo

11.2 Treatment discontinuation

In the subcutaneous VENTURE trial, treatment discontinuation rates were: placebo 14 percent, 2.5 mg 6 percent, 5.0 mg 11 percent, 10 mg 14 percent, 15 mg 20 percent. Discontinuation due to adverse events was 0 percent (placebo), 3 percent (2.5 mg), 11 percent (5.0 mg), 11 percent (10 mg), and 20 percent (15 mg) [1]. In the oral VENTURE-Oral trial, overall discontinuation was 28 percent for VK-2735-treated subjects versus 18 percent for placebo, with gastrointestinal events as the primary reason [6]. The 120 mg dose arm had a 38 percent discontinuation rate [6].

11.3 Serious adverse events

In the subcutaneous VENTURE trial, 12 treatment-emergent serious adverse events were reported across all arms, with no dose-dependent pattern: appendicitis, infected bite, head injury, limb injury, acute kidney injury, urinary incontinence, microcytic anemia, atrial fibrillation, cholecystitis, dehydration, paresthesia, and hypotension. Ten of 12 were assessed as unrelated to study drug; two events in one participant in the 5.0 mg arm (atrial fibrillation and dehydration) were assessed as possibly or probably related [1].

One death occurred in the 15 mg group (head trauma from a fall) and was assessed as unrelated to study drug [1].

In the Phase 1 subcutaneous trial, one serious adverse event (acute cholelithiasis in a subject with gallstone history) was reported [3].

11.4 Heart rate

Dose-dependent increases in heart rate were observed in the VENTURE trial: +3.3 to +9.3 beats per minute across active arms versus +1.4 beats per minute on placebo [1]. This finding is consistent with the incretin agonist class and has been observed

with semaglutide and tirzepatide. The clinical significance of the heart rate increase is under evaluation in the Phase 3 trials; no arrhythmias or cardiovascular events attributable to heart rate changes have been reported.

11.5 Anti-drug antibodies

Anti-drug antibodies were detected at Week 13 in 9 to 23 percent of participants across treatment groups in the VENTURE trial [1]. The clinical significance of anti-drug antibody formation has not been characterized; no relationship between antibody status and efficacy or safety was reported in the Phase 2 data.

11.6 Hypoglycemia

No hypoglycemia was reported in the Phase 1 or Phase 2 trials, consistent with the glucose-dependent mechanism of incretin-mediated insulin secretion [1, 3]. The Phase 3 VANQUISH-2 trial in patients with type 2 diabetes will provide additional hypoglycemia data in a population receiving concurrent antidiabetic medications.

11.7 Pregnancy and lactation

VK-2735 has not been studied in pregnant or lactating women. Based on the mechanism (weight loss during pregnancy is contraindicated) and the class precedent (semaglutide and tirzepatide carry pregnancy warnings), VK-2735 is expected to be contraindicated in pregnancy. Women of childbearing potential were required to use contraception during the Phase 2 trials.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative incretin-based pharmacotherapies against VK-2735, evaluated on five competency standards: novelty, effect size (weight loss), promising potential (current development state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal approved or late-stage investigational agents in the incretin receptor agonist class for obesity, with emphasis on compounds that share or differentiate from the VK-2735 dual GLP-1/GIP receptor agonist mechanism.

12.1 Tirzepatide (LY3298176; Mounjaro, Zepbound)

Mechanism: Dual GLP-1/GIP receptor agonist. A 39-amino-acid acylated peptide with a C20 fatty diacid moiety enabling weekly dosing. The compound is the closest mechanistic comparator to VK-2735, sharing the same receptor targets and the same structural class [12].

Development trajectory: Eli Lilly advanced tirzepatide through an extensive clinical development program. The SURMOUNT-1 Phase 3 trial (N=2,539) demonstrated 22.5 percent mean weight loss at the 15 mg dose at 72 weeks versus 2.4 percent on placebo [17]. Tirzepatide was approved by the FDA for type 2 diabetes (Mounjaro, May 2022) and for chronic weight management (Zepbound, November 2023).

Novelty: Low (relative to VK-2735). The dual GLP-1/GIP mechanism is shared with VK-2735. Tirzepatide was the first-in-class clinical development.

Effect size: The weight-loss efficacy of tirzepatide at 72 weeks (22.5 percent at the highest dose) is the benchmark against which VK-2735 will be measured. At comparable time points (13 weeks), the VK-2735 VENTURE data (14.7 percent) and the tirzepatide SURMOUNT data suggest broadly comparable early weight-loss trajectories, though direct cross-trial comparisons are confounded by differences in study design, population, and dose-titration protocols [1, 17].

Promising potential: High. Tirzepatide is approved and commercially available. Global sales exceeded \$10 billion annualized in 2025. The compound is the established market leader in the dual-agonist class.

Side-effect profile: Gastrointestinal adverse events (nausea, diarrhea, vomiting, constipation) are the principal tolerability limitation, occurring in 50 to 60 percent of participants at the highest dose in SURMOUNT trials. Rates are broadly comparable to VK-2735 Phase 2 data. Dose-dependent heart rate increases are observed. Rare pancreatitis and biliary events have been reported in postmarketing surveillance.

Overall validation: Very high. Multiple positive Phase 3 trials, regulatory approval in two indications, extensive postmarketing safety database.

Comparison to VK-2735: Tirzepatide is the established standard of care in the dual GLP-1/GIP agonist class. VK-2735 is positioned as a potential best-in-class successor with potential advantages in half-life (170 to 250 hours versus approximately 120 hours for tirzepatide), dosing flexibility (weekly, biweekly, monthly), and oral formulation availability. Head-to-head comparison data do not exist; the Phase 3 VANQUISH results will be the critical determinant of the competitive positioning of VK-2735 relative to tirzepatide.

12.2 Semaglutide (Wegovy, Ozempic, Rybelsus)

Mechanism: Selective GLP-1 receptor agonist. A 31-amino-acid acylated peptide with no GIP receptor activity [20].

Development trajectory: Novo Nordisk advanced semaglutide through the STEP Phase 3 program. The STEP 1 trial (N=1,961) demonstrated 14.9 percent mean weight loss at 2.4 mg weekly subcutaneous at 68 weeks versus 2.4 percent on placebo [20]. FDA approval: Wegovy (subcutaneous, obesity, June 2021), Ozempic (subcutaneous, type 2 diabetes, December 2017), Rybelsus (oral, type 2 diabetes, September 2019). Oral semaglutide at higher doses (50 mg daily) has demonstrated 15.1 percent weight loss for obesity in the OASIS-1 trial.

Novelty: Low. The selective GLP-1R agonist mechanism is well established and predates the dual-agonist class.

Effect size: Semaglutide at 2.4 mg weekly produces approximately 15 percent weight loss at 68 weeks. The addition of GIP receptor activity in tirzepatide and VK-2735 produces numerically greater weight loss (22 percent and 14.7 percent at 13 weeks, respectively) than semaglutide at comparable or shorter time points, supporting the dual-agonist advantage hypothesis [1, 17, 20].

Promising potential: High. Semaglutide is the most widely prescribed GLP-1R agonist globally and has generated extensive real-world safety and efficacy data.

Side-effect profile: Similar gastrointestinal adverse-event profile to the dual agonists (nausea, vomiting, diarrhea, constipation). Oral semaglutide (Rybelsus) requires strict fasting conditions for absorption, a limitation that VK-2735 oral formulation reportedly avoids [5, 9].

Overall validation: Very high. Multiple approved indications, extensive postmarketing database, cardiovascular outcome trial data (SELECT trial demonstrating 20 percent reduction in major adverse cardiovascular events).

Comparison to VK-2735: Semaglutide is the market-leading selective GLP-1R agonist. VK-2735 adds GIP receptor activity, which preclinical and clinical data suggest produces greater weight loss and metabolic improvement than GLP-1R agonism alone [2]. The VK-2735 oral formulation without food restrictions is a potential practical advantage over oral semaglutide.

12.3 Retatrutide (LY3437943)

Mechanism: Triple agonist of GLP-1R, GIPR, and GCGR. The glucagon receptor activation provides additional metabolic effects including increased hepatic fat oxidation and thermogenesis [18].

Development trajectory: Eli Lilly advanced retatrutide through Phase 2, demonstrating up to 24.2 percent mean weight loss at the 12 mg dose at 48 weeks in the Phase 2 trial (N=338) [18]. Phase 3 trials are ongoing with results expected in 2026 to 2027.

Novelty: High. The triple-agonist mechanism adds glucagon receptor activity to the dual GLP-1/GIP mechanism, representing a mechanistically distinct and more aggressive approach to metabolic modulation.

Effect size: The 24.2 percent weight loss at 48 weeks is the largest reported weight reduction in a Phase 2 obesity trial and exceeds the effects of both tirzepatide and semaglutide at comparable time points. If replicated in Phase 3, retatrutide would establish a new efficacy benchmark for the incretin agonist class.

Promising potential: High. Phase 3 ongoing. If Phase 3 data replicate Phase 2 efficacy, regulatory approval is anticipated in 2027 or 2028.

Side-effect profile: Gastrointestinal adverse events are the principal tolerability concern. The glucagon receptor activity introduces theoretical risks of hyperglycemia and hepatic effects that are absent from the dual GLP-1/GIP class.

Overall validation: Moderate. Strong Phase 2 data; Phase 3 data pending.

Comparison to VK-2735: Retatrutide is the most efficacious investigational compound in the obesity pipeline by Phase 2 weight-loss data. VK-2735 does not activate the glucagon receptor and therefore does not achieve the thermogenic and hepatic fat-oxidation effects of glucagon receptor agonism. However, VK-2735 avoids the theoretical liabilities of glucagon receptor activation and may have a more favorable safety profile. The relative positioning depends on the Phase 3 outcomes of both compounds.

12.4 Survodutide (BI 456906)

Mechanism: Dual GLP-1R/GCGR agonist. Unlike VK-2735, survodutide activates the glucagon receptor rather than the GIP receptor, providing a mechanistically distinct dual-agonist approach [19].

Development trajectory: Boehringer Ingelheim advanced survodutide through Phase 2 for obesity (up to 18.7 percent weight loss at 46 weeks) and Phase 3 for NASH. Phase 3 obesity trials are ongoing.

Novelty: Moderate. The GLP-1/glucagon dual-agonist mechanism is distinct from the GLP-1/GIP mechanism of VK-2735 and tirzepatide.

Effect size: Up to 18.7 percent weight loss at 46 weeks in Phase 2, intermediate between semaglutide (approximately 15 percent) and retatrutide (approximately 24 percent) at comparable timeframes.

Promising potential: Moderate to high. Phase 3 ongoing for both obesity and NASH indications.

Side-effect profile: Gastrointestinal adverse events consistent with the GLP-1R agonist class. The glucagon receptor component introduces similar theoretical considerations as retatrutide, though with single rather than dual non-GLP-1 receptor activation.

Overall validation: Moderate. Phase 2 data published; Phase 3 data pending.

Comparison to VK-2735: Survodutide and VK-2735 represent complementary approaches to dual incretin agonism: VK-2735 combines GLP-1 and GIP (the two incretin hormones), while survodutide combines GLP-1 and glucagon (an incretin and a counter-regulatory hormone). The GIP receptor activity of VK-2735 is expected to produce more favorable effects on adipose tissue metabolism and insulin sensitivity, while the glucagon receptor activity of survodutide is expected to produce greater hepatic fat reduction and thermogenesis. The Phase 3 outcomes of both compounds will clarify the relative clinical merits of each approach.

12.5 Orforglipron (LY3502970; Foundayo)

Mechanism: Oral non-peptide GLP-1R agonist. Unlike VK-2735 (a peptide), orforglipron is a small molecule that activates GLP-1R without requiring peptide backbone engineering or acylation for oral bioavailability [21].

Development trajectory: Eli Lilly advanced orforglipron through Phase 3 trials, demonstrating up to 14.7 percent weight loss at 36 weeks in the Phase 2 trial (N=272). The compound received FDA approval in 2025 as the first oral non-peptide GLP-1R agonist for obesity.

Novelty: High. The non-peptide oral GLP-1R agonist mechanism is a structurally distinct approach that bypasses the bioavailability limitations of oral peptide therapeutics.

Effect size: Approximately 14.7 percent weight loss at 36 weeks in Phase 2. The compound activates only GLP-1R (no GIP activity), and effect sizes are therefore expected to be comparable to injectable semaglutide rather than to the dual agonists.

Promising potential: High. Approved and commercially available as the first oral small-molecule GLP-1R agonist.

Side-effect profile: Gastrointestinal adverse events consistent with the GLP-1R agonist class. The oral route avoids injection-site reactions.

Overall validation: High. Phase 3 data supporting approval; early postmarketing experience.

Comparison to VK-2735: Orforglipron and VK-2735 oral both target the oral obesity therapeutic market but through different approaches: orforglipron is a non-peptide small molecule with GLP-1R selectivity, while VK-2735 oral is a peptide tablet with dual GLP-1/GIP activity. VK-2735 oral has the theoretical advantage of dual-receptor agonism (greater weight loss potential) and the practical advantage of reported absorption without food restrictions. Orforglipron has the advantage of established approval and the structural simplicity and scalability of small-molecule manufacturing.

12.6 Comparator summary

The five comparators span the spectrum of incretin-based obesity pharmacotherapy. **Tirzepatide** is the established dual GLP-1/GIP agonist with regulatory approval and the closest mechanistic comparator to VK-2735; the competitive differentiation of VK-2735 rests on potential advantages in half-life, dosing flexibility, and oral formulation. **Semaglutide** is the market-leading selective GLP-1R agonist and the efficacy baseline against which dual agonists are measured; VK-2735 adds GIP receptor activity for potentially greater weight loss. **Retatrutide** is the most efficacious investigational compound by Phase 2 data through triple-receptor activation; VK-2735 does not match the glucagon receptor component but may have safety advantages. **Survodutide** represents the alternative dual-agonist strategy (GLP-1/glucagon rather than GLP-1/GIP); comparative Phase 3 data will clarify relative merits. **Orforglipron** is the first approved oral non-peptide GLP-1R agonist; VK-2735 oral competes with dual-receptor activity but faces the bioavailability challenges inherent to oral peptide delivery.

VK-2735 occupies a differentiated position in this competitive landscape: it is the only investigational dual GLP-1/GIP agonist with both injectable and oral formulations in late-stage development, it has the longest half-life among the dual agonists (enabling potential monthly dosing), and it has produced Phase 2 weight-loss data that are competitive with the early trajectories of tirzepatide at comparable time points. The Phase 3 VANQUISH data, expected in 2026 to 2027, will be the critical determinant of whether VK-2735 achieves the best-in-class positioning that the Phase 2 data suggest is attainable.

13. References

1. Bays HE, Toth P, Alkhouri N, et al. Weekly subcutaneous VK2735, a GIP/GLP-1 receptor dual agonist, for weight management: Phase 2, randomized, 13-week VENTURE study. *Obesity (Silver Spring)*. 2026;34(3):537-549. doi:10.1002/oby.70106.
2. Viking Therapeutics. Preclinical characterization of dual GLP-1/GIP receptor agonist series in diet-induced obese mice. Presented at ObesityWeek 2021.
3. Viking Therapeutics. Viking Therapeutics announces results from Phase 1 clinical trial of dual GLP-1/GIP receptor agonist VK2735. Press release, March 28, 2023.
4. Viking Therapeutics. Viking Therapeutics presents new data from Phase 1 clinical trial of dual GLP-1/GIP receptor agonist VK2735. Presented at ObesityWeek 2023, October 2023.
5. Viking Therapeutics. Viking Therapeutics announces results from Phase 1 clinical trial of oral tablet formulation of dual GLP-1/GIP receptor agonist VK2735. Press release, March 26, 2024.
6. Viking Therapeutics. Viking Therapeutics announces positive top-line results from Phase 2 VENTURE-Oral dosing trial of VK2735 tablet formulation in patients with obesity. Press release, August 19, 2025.
7. Viking Therapeutics. Viking Therapeutics announces completion of enrollment in Phase 3 VANQUISH-1 trial of VK2735. Press release, December 2025.
8. Viking Therapeutics. Viking Therapeutics announces completion of enrollment in Phase 3 VANQUISH-2 trial of VK2735. Press release, March 26, 2026.
9. PepCodex. VK2735: GLP-1/GIP dual agonist research. 2026. Available at: <https://www.pepcodex.com/peptides/vk2735>.
10. Lau J, Bloch P, Schaffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58(18):7370-7380.
11. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab*. 2018;27(4):740-756.

12. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216.
13. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.
14. Turton MD, O'Shea D, Gunn I, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature*. 1996;379(6560):69-72.
15. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17(6):819-837.
16. Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab*. 2020;31(6):410-421.
17. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity (SURMOUNT-1). *N Engl J Med*. 2022;387(3):205-216.
18. Jastreboff AM, Kaplan LM, Frias JP, et al. Triple-hormone-receptor agonist retatrutide for obesity: a Phase 2 trial. *N Engl J Med*. 2023;389(6):514-526.
19. Gastaldelli A, Cusi K, Fernandez Lando L, et al. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI). *Lancet Diabetes Endocrinol*. 2022;10(6):393-406.
20. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity (STEP 1). *N Engl J Med*. 2021;384(11):989-1002.
21. Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N Engl J Med*. 2023;389(10):877-888.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. VK-2735 is an investigational compound that is not approved by any regulatory authority for any indication. The compound is available only through clinical trial enrollment or as a research-grade preparation from chemical suppliers; investigators should obtain analytical confirmation of identity and purity on every lot. Clinical data cited in this monograph are

derived from Phase 1 and Phase 2 trials with limited sample sizes and treatment durations; Phase 3 registration data are pending and will be required for definitive assessment of efficacy and safety.