

Maritide

A first-in-class bispecific antibody-peptide conjugate developed at Amgen that pairs a fully human monoclonal glucose-dependent insulintropic polypeptide receptor antagonist antibody with two covalently linked glucagon-like peptide 1 analogue agonist peptides, yielding a long-acting once-monthly injectable for chronic weight management distinguished from existing incretin therapeutics by simultaneous GIP receptor blockade and an approximately 21-day elimination half-life.

DOCUMENT	KDC-MN-1412
ISSUED	2026-05-10
REVISION	1.0
AUTHOR	Kodi ac bio l abs Research
COMPOUND CLASS	Bispecific peptide-antibody conjugate combining GLP-1 receptor agonism with GIP receptor antagonism

ABSTRACT

Maridebart cafraglutide (MariTide; development code AMG 133) is a first-in-class bispecific peptide-antibody conjugate engineered at Amgen by covalent attachment of two glucagon-like peptide 1 (GLP-1) receptor agonist peptide analogues to a fully human immunoglobulin G2 (IgG2) monoclonal antibody that functions as a potent antagonist of the glucose-dependent insulintropic polypeptide receptor (GIPR). The molecule was designed to exploit the additive weight-loss pharmacology of simultaneous GLP-1 receptor (GLP-1R) activation and GIP receptor blockade, a mechanistic combination that in preclinical diet-induced obese mouse and cynomolgus monkey models produced greater body-weight reduction than either moiety alone. In cell-based functional assays the compound demonstrates GLP-1R agonist activity with EC₅₀ values of 24.4 picomolar (human), 5.7 picomolar (cynomolgus monkey), 2.4 picomolar (rat), and 123 picomolar (mouse), and GIPR antagonist activity with IC₅₀ values of 46.4 nanomolar (human), 26.5 nanomolar (cynomolgus monkey), and 822.3 nanomolar (rat) [1, 2]. The antibody scaffold confers a terminal elimination half-life of approximately 21 days in humans after subcutaneous administration, approximately three-fold longer than the longest-acting approved once-weekly GLP-1 receptor agonists, and supports once-monthly or less frequent dosing [1]. In a Phase 1 randomized, double-blind, placebo-controlled single- and multiple-ascending-dose study (NCT04478708) in 163 adults with obesity, maridebart cafraglutide produced dose-dependent weight loss of up to 14.5 percent at 12 weeks with weight loss maintained for up to 150 days after the final dose, accompanied by an acceptable safety and tolerability

profile in which gastrointestinal adverse events (nausea, vomiting) were predominantly mild and transient [1]. A Phase 2 dose-ranging study (NCT05669599) in 592 adults with obesity with or without type 2 diabetes randomized to subcutaneous maridebart cafraglutide at 140, 280, or 420 mg every four weeks or 420 mg every eight weeks versus placebo for 52 weeks demonstrated mean weight loss of 12.3 to 20 percent in participants without type 2 diabetes and 8.4 to 17 percent in participants with type 2 diabetes, with HbA1c reductions of up to 2.2 percentage points, without evidence of a weight-loss plateau at 52 weeks [3, 4]. The Phase 2 study further reported no clinically significant changes in bone mineral density and body-composition data indicating that the majority of weight lost was fat mass rather than lean tissue. Gastrointestinal adverse events were the most common treatment-emergent events and were mitigated by dose escalation from a lower starting dose; discontinuation rates due to gastrointestinal events were approximately 8 percent with dose escalation compared with 12 to 27 percent without [3, 4]. Amgen initiated the Phase 3 MARITIME program in 2025, comprising chronic weight management trials (MARITIME-1 in obesity without type 2 diabetes, MARITIME-2 in obesity with type 2 diabetes) with planned 72-week treatment duration and primary readouts expected in early 2027, as well as planned Phase 3 cardiovascular outcomes, heart failure, and obstructive sleep apnea studies [5, 6]. The compound is not approved by any regulatory authority as of the monograph date. This monograph documents the molecular design and structural biology of the peptide-antibody conjugate; the dual-receptor pharmacology at GLP-1R and GIPR in molecular and cellular detail; the preclinical pharmacology in rodent and primate models; the comprehensive human pharmacokinetic record; the clinical evidence base across

Phase 1 and Phase 2 obesity and type 2 diabetes endpoints; sourcing and handling considerations; stack-interaction implications; adverse-event profile; and a comparative assessment of five incretin-class obesity therapeutics against maridebart cafraglutide on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Maridebart cafraglutide.

Trade name (proposed): MariTide (Amgen).

Development code: AMG 133 (Amgen). The development code is the canonical identifier in the preclinical and Phase 1 pharmacology literature and the identifier under which the seminal Veniant et al. (2024) Nature Metabolism publication was conducted [1].

Chemical Abstracts Service registry number: Not assigned at monograph date. As a biologic (antibody-peptide conjugate), maridebart cafraglutide does not carry a conventional small-molecule CAS registry number. The DrugBank accession number is DB19339 [7].

IUPHAR/BPS Guide to Pharmacology ligand identifier: 13316 [8].

ClinicalTrials.gov identifiers: NCT04478708 (Phase 1, single and multiple ascending dose); NCT05669599 (Phase 2, dose-ranging in obesity with and without type 2 diabetes); NCT06858878 (Phase 3, MARITIME-1); NCT07037433 (Phase 3, cardiovascular outcomes) [3, 5, 9].

1.2 Structural class and molecular architecture

Maridebart cafraglutide is a bispecific peptide-antibody conjugate (sometimes classified as an antibody-drug conjugate or antibody-peptide conjugate) comprising three functional domains: a fully human immunoglobulin G2 (IgG2) monoclonal antibody that binds and antagonizes the human glucose-dependent insulintropic polypeptide receptor (GIPR) at its extracellular domain, and two GLP-1 analogue agonist peptides covalently linked to the antibody through engineered amino acid linkers [1, 2].

Antibody component (maridebart): A fully human IgG2 monoclonal antibody selected for high-affinity binding to the extracellular domain of human GIPR. The IgG2 isotype was selected to minimize Fc-gamma receptor engagement and comple-

ment activation, consistent with the intended pharmacological activity (receptor antagonism without cytotoxicity). The antibody blocks GIP-mediated receptor activation with an IC₅₀ of 46.4 nanomolar against human GIPR in cell-based cAMP assays [2].

Peptide component (cafraglutide): Two GLP-1 analogue peptides, each a modified exendin-4-derived sequence optimized for GLP-1R binding affinity and resistance to dipeptidyl peptidase IV (DPP-IV) cleavage, conjugated through amino acid linkers to defined positions on the antibody heavy chain. Each peptide activates the human GLP-1 receptor with an EC₅₀ of 24.4 picomolar in cell-based cAMP assays [2].

Molecular weight: Approximately 153,514 daltons (intact conjugate) [7].

Physical properties: The compound is formulated as a sterile liquid for subcutaneous injection. As a protein-peptide conjugate, it requires cold-chain storage (2 to 8 degrees Celsius) and is not amenable to conventional small-molecule characterization methods (melting point, solubility in organic solvents). Higher-order structural characterization is by size-exclusion chromatography, capillary electrophoresis, and mass spectrometry.

1.3 Design and synthesis

The Amgen team evaluated more than 150 structural variants of antibody-peptide conjugate molecules during the lead optimization campaign before selecting AMG 133 as the clinical candidate [10]. The design rationale was informed by human genetic data linking GIPR loss-of-function variants to lower body mass index and by preclinical evidence that GIPR antagonism combined with GLP-1R agonism produced additive or synergistic weight loss exceeding either mechanism alone in diet-induced obese mice [1, 11].

The synthesis of maridebart cafraglutide follows recombinant biologic manufacturing procedures: the anti-GIPR IgG2 antibody is expressed in Chinese hamster ovary (CHO) cells, purified by protein A affinity chromatography and ion-exchange chromatography, and characterized for identity, purity, and potency. The GLP-1 analogue peptides are produced by solid-phase peptide synthesis or recombinant expression, purified by reversed-phase high-performance liquid chromatography, and conjugated to the antibody through site-specific amino acid linker chemistry. The final conjugate is characterized by size-exclusion chromatography (to confirm

molecular weight and aggregation state), liquid chromatography-mass spectrometry (to confirm peptide-to-antibody ratio), capillary electrophoresis (to confirm charge variants), and cell-based potency assays at both GLP-1R and GIPR [1, 2].

The compound is manufactured at Amgen biologic production facilities. It is not synthesizable by conventional small-molecule chemical methods and is not available as a research-grade chemical from standard chemical suppliers as of monograph date.

2. Abstract

Maridebart cafraglutide (MariTide; AMG 133) is a first-in-class bispecific peptide-antibody conjugate that combines glucagon-like peptide 1 receptor (GLP-1R) agonism with glucose-dependent insulintropic polypeptide receptor (GIPR) antagonism in a single molecule engineered for once-monthly subcutaneous administration [1]. The compound was developed at Amgen on the basis of human genetic evidence and preclinical pharmacology demonstrating that simultaneous GLP-1R activation and GIPR blockade produces greater body-weight reduction than either mechanism alone in diet-induced obese animal models [1, 11].

The molecular architecture pairs a fully human IgG2 monoclonal antibody targeting the GIPR extracellular domain with two covalently conjugated GLP-1 analogue agonist peptides, yielding a compound with potent dual-receptor activity (GLP-1R EC₅₀ 24.4 picomolar; GIPR IC₅₀ 46.4 nanomolar in human cell-based assays) and a terminal elimination half-life of approximately 21 days in humans, approximately three-fold longer than the longest-acting approved weekly GLP-1 receptor agonists [1, 2].

The clinical development program has advanced through Phase 1 and Phase 2 studies with consistent demonstration of dose-dependent, clinically meaningful weight loss. In the Phase 1 study (NCT04478708), multiple ascending doses of maridebart cafraglutide produced weight loss of up to 14.5 percent at 12 weeks, with weight loss maintained for up to 150 days after the final dose [1]. In the Phase 2 dose-ranging study (NCT05669599), 52-week treatment at doses of 140 to 420 mg every four weeks produced mean weight loss of 12.3 to 20 percent in adults with obesity and 8.4 to 17 percent in adults with obesity and type 2 diabetes, without evidence of a weight-loss plateau, and with HbA1c reductions of up to 2.2 percentage points in the diabetic cohort [3, 4]. No clinically significant changes in bone mineral density were observed, and body-composition analyses indicated that the majority of weight lost was adipose tissue [3]. Gastrointestinal adverse events (nausea, vomiting, constipation) were the most frequent treatment-emergent events but were predominantly mild and transient, with prevalence substantially reduced by dose-escalation protocols [3, 4].

The compound mechanism is distinguished from tirzepatide (a dual GLP-1R and GIPR agonist) by the antagonism rather than agonism at the GIPR, representing a fundamentally different approach to incretin pharmacology in obesity. The approximately 21-day half-life is distinguished from all approved incretin therapeutics and supports once-monthly dosing, a potential adherence advantage over weekly injection regimens [1].

Amgen initiated the Phase 3 MARITIME clinical program in 2025, comprising registration-directed chronic weight management trials and planned cardiovascular outcomes, heart failure, and obstructive sleep apnea studies, with primary readouts expected beginning in early 2027 [5, 6]. The compound is not approved by any regulatory authority and is classified as an investigational biologic.

3. Discovery and Development History

3.1 Origin and scientific rationale

Maridebart cafraglutide was conceived within Amgen's metabolic disease research division on the basis of converging evidence from human genetics and incretin biology. Large-scale genome-wide association studies had identified GIPR loss-of-function variants as associated with lower body mass index and reduced adiposity in population cohorts, suggesting that pharmacological GIPR antagonism might produce clinically meaningful weight reduction [11, 12]. Concurrently, GLP-1 receptor agonism had been validated as a weight-loss mechanism by semaglutide, liraglutide, and tirzepatide clinical programs. The Amgen team hypothesized that combining GIPR antagonism with GLP-1R agonism in a single molecule would produce additive or synergistic weight loss exceeding either mechanism alone, a hypothesis subsequently confirmed in diet-induced obese mouse models where the combination of an anti-mouse GIPR antibody with liraglutide produced 23.5 percent body-weight reduction versus smaller reductions with either agent alone [1].

3.2 Lead optimization

The design of the clinical candidate proceeded through systematic evaluation of more than 150 antibody-peptide conjugate variants, exploring antibody isotype (IgG1 versus IgG2), peptide identity and length, linker chemistry and attachment site, peptide-to-antibody ratio, and in vitro potency at both target receptors [10]. The selected candidate (AMG 133) carried two GLP-1 analogue peptides per antibody molecule, achieved picomolar GLP-1R agonist potency and nanomolar GIPR antagonist potency in human cell-based assays, and demonstrated favorable pharmacokinetic properties in cynomolgus monkeys (long half-life consistent with the IgG2 scaffold, subcutaneous bioavailability suitable for injection-site delivery) [1, 2].

3.3 Preclinical development

AMG 133 entered formal preclinical development with good laboratory practice toxicology studies in rodents and cynomolgus monkeys. The preclinical safety profile supported advancement to clinical testing. The compound demonstrated dose-dependent weight loss and improvements in glucose tolerance, fasting insulin, and lipid parameters in diet-induced obese mice and in spontaneously obese cynomolgus monkeys [1].

3.4 Phase 1 clinical development

The first-in-human Phase 1 study (NCT04478708) was a randomized, double-blind, placebo-controlled single-ascending-dose and multiple-ascending-dose trial initiated in 2020 in 163 adults with obesity (body mass index 30 to 40 kg/m²) at clinical sites in the United States. Single ascending doses of 21 to 420 mg and multiple ascending doses (three or six doses at 70 to 420 mg every four weeks) were evaluated. The study reported dose-dependent weight loss up to 14.5 percent at 12 weeks in the multiple-ascending-dose cohorts, an acceptable safety and tolerability profile, predominantly mild and transient gastrointestinal adverse events, and weight loss maintained for up to 150 days after the last dose [1]. No severe or serious adverse events leading to study drug discontinuation were reported, and no cases of treatment-related hypoglycemia were observed. The results were published in *Nature Metabolism* in February 2024 (Veniant et al.) [1].

3.5 Phase 2 clinical development

The Phase 2 dose-ranging study (NCT05669599; MARITIME-1 Part 1) was a double-blind, randomized, placebo-controlled trial in 592 adults (465 with obesity alone, 127 with obesity and type 2 diabetes) initiated in 2023 at approximately 80 clinical sites across the United States, Europe, and Asia-Pacific. Participants were randomized to subcutaneous maridebart cafraglutide at 140, 280, or 420 mg every four weeks (with or without dose escalation), 420 mg every eight weeks, or placebo for 52 weeks [3, 4]. Topline results were announced by Amgen in November 2024, with full results presented at the American Diabetes Association 85th Scientific Sessions in June 2025 and published in the *New England Journal of Medicine* [3, 4].

3.6 Phase 3 clinical development and current status

Amgen initiated the Phase 3 MARITIME clinical program in 2025. The core registration trials are MARITIME-1 (NCT06858878; chronic weight management in adults with obesity or overweight without type 2 diabetes) and MARITIME-2 (chronic weight management in adults with obesity or overweight with type 2 diabetes), each a 72-week, randomized, double-blind, placebo-controlled study [5, 6]. Amgen has also announced planned Phase 3 studies evaluating maridebart cafraglutide for cardiovascular outcomes in atherosclerotic cardiovascular disease (ASCVD), heart failure, and obstructive sleep apnea [5, 6]. Primary readouts from the core weight management trials are expected in early 2027 [6]. The compound is not approved by any regulatory authority as of the monograph date.

4. Mechanism of Action

Maridebart cafraglutide is a bispecific molecule with two distinct pharmacological activities expressed simultaneously: agonism at the GLP-1 receptor and antagonism at the GIP receptor. These activities are mediated by separate structural domains of the molecule (the conjugated peptides and the antibody, respectively) and engage distinct signaling pathways in target tissues.

4.1 GLP-1 receptor agonism

The glucagon-like peptide 1 receptor (GLP-1R) is a class B G-protein-coupled receptor expressed on pancreatic beta cells, hypothalamic and brainstem neurons (including the arcuate nucleus, area postrema, and nucleus tractus solitarius), vagal afferents, gastric parietal and chief cells, cardiomyocytes, and vascular endothelium [13]. GLP-1R activation stimulates adenylyl cyclase through Gs-protein coupling, elevating intracellular cyclic adenosine monophosphate (cAMP) and activating protein kinase A and exchange protein activated by cAMP (Epac) downstream cascades.

The two GLP-1 analogue peptides conjugated to the maridebart antibody activate the human GLP-1R with an EC₅₀ of 24.4 picomolar in cell-based cAMP accumulation assays, comparable to or more potent than the GLP-1R agonist activities of semaglutide and tirzepatide [2]. The peptides are modified exendin-4-derived sequences engineered for resistance to DPP-IV proteolysis, a modification that is functionally redundant given the antibody-scaffold protection from renal clearance but that ensures that any peptide liberated by linker degradation retains agonist activity.

The principal therapeutic consequences of GLP-1R agonism relevant to the obesity indication are: (a) central appetite suppression through activation of hypothalamic pro-opiomelanocortin (POMC) neurons and inhibition of neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons in the arcuate nucleus, and through direct activation of area postrema neurons that relay satiety signals to the nucleus tractus solitarius; (b) delayed gastric emptying through vagal efferent modulation; (c) glucose-dependent insulin secretion from pancreatic beta cells (the incretin effect); and (d) suppression of glucagon secretion from pancreatic alpha cells [13, 14].

The GLP-1R agonist component is also the principal source of the gastrointestinal adverse-event profile (nausea, vomiting), which reflects activation of area postrema neurons and delayed gastric motility.

4.2 GIP receptor antagonism

The glucose-dependent insulinotropic polypeptide receptor (GIPR) is a class B G-protein-coupled receptor expressed on pancreatic beta cells, adipocytes (white and brown), osteoblasts, osteoclasts, hypothalamic neurons, and gastric and intestinal enteroendocrine cells [15, 16]. GIP is secreted by enteroendocrine K-cells in response to nutrient ingestion and acts as an incretin hormone (stimulating glucose-dependent insulin secretion) and as a direct regulator of lipid metabolism in adipose tissue.

The maridebart antibody component binds the extracellular domain of human GIPR with high affinity and blocks GIP-mediated receptor activation with an IC₅₀ of 46.4 nanomolar in cell-based cAMP assays [2]. The antagonism prevents GIP-stimulated lipogenesis in adipocytes, GIP-mediated promotion of adipose tissue expansion, and GIP-driven nutrient-dependent insulin secretion beyond the magnitude maintained by GLP-1R agonism alone [15, 16].

The rationale for GIPR antagonism (rather than the GIPR agonism employed by tirzepatide) derives from multiple convergent lines of evidence. First, human genetic studies have identified GIPR coding variants with reduced receptor function (loss-of-function or reduced-function alleles) as associated with lower body mass index, reduced waist-to-hip ratio, and protection from obesity [11, 12]. Second, GIPR knockout mice are resistant to diet-induced obesity and exhibit reduced adipose tissue mass on high-fat diets [17]. Third, GIP acts directly on white adipocytes to stimulate glucose uptake, lipoprotein lipase activity, and triglyceride storage, effects that pharmacological GIPR antagonism would be expected to oppose [15, 16]. Fourth, central nervous system GIPR blockade has been demonstrated to enhance the anorectic efficacy of GLP-1R agonism in mouse models, with a 2025 *Nature Metabolism* study reporting that the additive weight loss produced by an anti-GIPR antibody conjugated to GLP-1 analogues requires both brain GIPR and brain GLP-1R for maximal effect [18].

The intellectual tension between GIPR agonism (tirzepatide approach) and GIPR antagonism (maridebart cafraglutide approach) remains an active area of investigation. A 2020 *Nature Communications* study demonstrated that chronic GIPR ago-

nism desensitizes adipocyte GIPR activity, functionally mimicking GIPR antagonism and suggesting that both pharmacological approaches may converge on a common downstream phenotype of reduced GIP signaling in adipose tissue [19]. Whether this convergence extends to the central nervous system, where GIPR agonism and antagonism may produce qualitatively different effects on appetite regulation, is an open question informing the interpretation of clinical efficacy differences between the two approaches.

4.3 Composite pharmacology and the additive weight-loss hypothesis

The composite pharmacology of maridebart cafraglutide produces weight loss through at least three convergent mechanisms: (a) GLP-1R-mediated central appetite suppression and delayed gastric emptying; (b) GIPR-antagonism-mediated reduction in adipose tissue lipogenesis and nutrient storage; and (c) central nervous system GIPR blockade that enhances GLP-1R-driven satiety signaling [1, 18].

In preclinical diet-induced obese mouse models, the combination of an anti-mouse GIPR antibody with the GLP-1R agonist liraglutide produced 23.5 percent body-weight reduction, substantially exceeding the weight loss produced by either the anti-GIPR antibody alone (approximately 8 to 12 percent) or liraglutide alone (approximately 10 to 15 percent) [1]. The additive effect was confirmed in cynomolgus monkeys, where AMG 133 produced dose-dependent weight loss and improvements in metabolic parameters exceeding those produced by GLP-1R agonism alone [1].

The clinical translation of this additive pharmacology is reflected in the Phase 2 weight-loss data, where maridebart cafraglutide at the highest studied dose produced up to 20 percent mean weight loss at 52 weeks without a weight-loss plateau, a magnitude that compares favorably with the 52-week weight loss reported for tirzepatide (approximately 20 to 22 percent at the highest dose in the SURMOUNT-1 trial) despite the monthly rather than weekly dosing frequency [3, 20].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Maridebart cafraglutide is administered by subcutaneous injection. As a high-molecular-weight biologic (approximately 153,514 daltons), absorption from the subcutaneous injection site is slow and mediated by lymphatic drainage rather than direct capillary absorption. Time to peak plasma concentration (Tmax) after a single subcutaneous dose is approximately 3 to 7 days, consistent with the absorption kinetics of other IgG-based therapeutics [1].

Subcutaneous bioavailability has not been reported in published form as an absolute value but is inferred from dose-proportional pharmacokinetics in the Phase 1 study to be consistent with the approximately 50 to 80 percent range typical of IgG-based subcutaneous biologics [1].

5.2 Distribution

As an IgG2-based molecule, maridebart cafraglutide distributes primarily in the vascular and interstitial fluid compartments. The volume of distribution is expected to be in the range of 3 to 8 liters (central compartment), consistent with IgG therapeutics. Distribution to the central nervous system occurs through receptor-mediated transcytosis and limited passive diffusion across the blood-brain barrier; the 2025 Nature Metabolism study by Lu et al. provided evidence that the GIPR-antagonist antibody component requires central nervous system access for the additive weight-loss effect, supporting functional brain penetration at pharmacologically relevant levels [18].

Plasma protein binding is not conventionally measured for IgG-based therapeutics, which circulate predominantly as intact immunoglobulin molecules and are not subject to albumin binding dynamics.

5.3 Metabolism and elimination

The terminal elimination half-life of maridebart cafraglutide in humans is approximately 21 days (approximately 504 hours) after subcutaneous administration [1]. This half-life, approximately three-fold longer than the 5- to 7-day half-lives of once-weekly GLP-1 receptor agonists (semaglutide, tirzepatide), is conferred by the IgG2 antibody scaffold and its interaction with the neonatal Fc receptor (FcRn), which mediates IgG recycling and extends serum residence through pH-dependent binding in endosomes [21].

Elimination proceeds through the standard IgG catabolism pathway: pinocytic uptake into endothelial and reticuloendothelial cells, acidification in endosomes, FcRn-mediated recycling of a fraction of the internalized IgG back to the cell surface, and lysosomal degradation of the non-recycled fraction to amino acids. The GLP-1 analogue peptides are degraded concomitantly with the antibody scaffold. There is no hepatic cytochrome P450-mediated metabolism and no renal filtration of the intact molecule [21].

The long half-life supports once-monthly subcutaneous dosing at steady state. Steady-state plasma concentrations are achieved after approximately 3 to 4 doses (12 to 16 weeks) on a monthly dosing regimen, consistent with the approximately five-half-life accumulation rule.

5.4 Routes of administration

The only clinically studied route is subcutaneous injection. Maridebart cafraglutide is formulated as a liquid in a prefilled autoinjector device intended for patient self-administration [5, 6]. Intravenous administration has been studied in Phase 1 for pharmacokinetic characterization but is not the intended clinical route. Oral administration is not feasible owing to the protein nature of the molecule and its susceptibility to gastrointestinal proteolysis.

5.5 Special populations

Published pharmacokinetic data in special populations (renal impairment, hepatic impairment, elderly, pediatric) are not yet available. As an IgG-based biologic eliminated by catabolism rather than renal or hepatic clearance, maridebart cafraglutide is not expected to require dose adjustment for renal or hepatic impairment,

consistent with the pharmacokinetic behavior of other IgG-based therapeutics. Pediatric and geriatric pharmacokinetics will be characterized in the Phase 3 program and in dedicated pharmacokinetic studies.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Maridebart cafraglutide demonstrates potent dual-receptor activity in cell-based functional assays. GLP-1R agonist activity (cAMP accumulation in GLP-1R-expressing cells) yields EC₅₀ values of 24.4 picomolar (human), 5.7 picomolar (cynomolgus monkey), 2.4 picomolar (rat), and 123 picomolar (mouse) [2]. GIPR antagonist activity (inhibition of GIP-stimulated cAMP accumulation in GIPR-expressing cells) yields IC₅₀ values of 46.4 nanomolar (human), 26.5 nanomolar (cynomolgus monkey), and 822.3 nanomolar (rat) [2]. The species differences in GIPR antagonist potency reflect sequence divergence in the GIPR extracellular domain between human, primate, and rodent orthologs.

The compound does not exhibit agonist activity at the glucagon receptor, distinguishing it from triple-agonist molecules such as retatrutide.

6.2 Diet-induced obese mouse models

In diet-induced obese C57BL/6 mice, once-weekly subcutaneous administration of AMG 133 for 4 to 8 weeks produced dose-dependent reductions in body weight, with maximum weight loss exceeding 20 percent of baseline body weight at the highest studied doses [1]. The combination of an anti-mouse GIPR antibody with liraglutide produced 23.5 percent body-weight reduction, significantly greater than either agent alone, confirming the additive weight-loss hypothesis [1]. Treated animals showed improved glucose tolerance on intraperitoneal glucose tolerance testing, reduced fasting insulin, and reduced hepatic steatosis on histological examination.

6.3 Cynomolgus monkey studies

In spontaneously obese cynomolgus monkeys, subcutaneous AMG 133 administered once weekly for 8 to 12 weeks produced dose-dependent body-weight reduction and improvements in fasting glucose, insulin, and triglycerides [1]. The pri-

mate studies confirmed that the dual mechanism translated across species and provided pharmacokinetic and safety data supporting the selection of the subcutaneous route and the monthly dosing interval for clinical development.

6.4 Central nervous system mechanism studies

A 2025 study by Lu et al. published in Nature Metabolism demonstrated that the additive weight-loss effect of the GIPR-antagonist antibody conjugated to GLP-1 analogues requires both brain GIPR and brain GLP-1R for maximal efficacy in diet-induced obese mice [18]. Conditional knockout of GIPR in the central nervous system attenuated the weight-loss response to the antibody-peptide conjugate, confirming that GIPR blockade in the brain contributes to the overall pharmacological effect beyond the peripheral adipose tissue mechanism. This finding has implications for the interpretation of the clinical weight-loss data and for the positioning of the compound relative to GIPR agonists, which may produce distinct central effects.

7. Clinical Evidence Base

7.1 Phase 1 study (NCT04478708)

The first-in-human study was a randomized, double-blind, placebo-controlled, single-ascending-dose (SAD) and multiple-ascending-dose (MAD) trial conducted at clinical sites in the United States in 163 adults with obesity (body mass index 30 to 40 kg/m²) without type 2 diabetes [1]. SAD cohorts received single subcutaneous doses of 21, 70, 140, 210, 280, or 420 mg. MAD cohorts received three or six doses at 70, 140, 210, 280, or 420 mg administered every four weeks.

Weight loss was dose-dependent and clinically meaningful. In the MAD cohorts, participants receiving six doses at 420 mg achieved mean weight loss of approximately 14.5 percent from baseline at 12 weeks [1]. Weight loss was maintained for up to 150 days (approximately 5 months) after the final dose, and maximum weight loss was maintained for approximately 2 months after the last dose, reflecting the long elimination half-life and the sustained pharmacodynamic effect [1].

Safety findings included mild and transient gastrointestinal adverse events (nausea, vomiting), predominantly occurring within 48 hours of dose administration and resolving spontaneously. No severe or serious adverse events attributable to the study drug were reported. No treatment-related hypoglycemia was observed. Injection-site reactions were uncommon and mild [1].

The Phase 1 results were published by Veniant et al. in *Nature Metabolism* in February 2024 [1].

7.2 Phase 2 study (NCT05669599)

The Phase 2 dose-ranging study enrolled 592 adults across two cohorts: 465 with obesity (body mass index 30 or greater, or 27 or greater with at least one weight-related comorbidity) without type 2 diabetes, and 127 with obesity and type 2 diabetes [3, 4]. The study was double-blind, randomized, and placebo-controlled with an active treatment duration of 52 weeks.

Participants in the obesity cohort were randomized to maridebart cafraglutide at 140, 280, or 420 mg every four weeks without dose escalation; 420 mg every eight weeks without dose escalation; 420 mg every four weeks with 4-week dose escalation (starting at 140 mg); 420 mg every four weeks with 12-week dose escalation (starting at 140 mg); or placebo. Participants in the obesity with type 2 diabetes cohort were randomized to 140, 280, or 420 mg every four weeks without dose escalation or placebo [3, 4].

Efficacy in obesity without type 2 diabetes: Mean body-weight change from baseline at 52 weeks ranged from minus 12.3 percent to minus 16.2 percent across the dose groups in the treatment-policy estimand (intention-to-treat) analysis, compared with minus 2.6 percent in the placebo arm. In the trial-product estimand (on-treatment, adherent population), weight loss ranged from minus 16.3 percent to minus 20 percent [3, 4]. A weight-loss plateau was not reached at 52 weeks, with the weight trajectory continuing downward at the final assessment, indicating that longer treatment duration would be expected to produce additional weight reduction.

Efficacy in obesity with type 2 diabetes: Mean body-weight change from baseline at 52 weeks ranged from minus 8.4 percent to minus 12.3 percent across dose groups (treatment-policy), compared with minus 1.4 percent in the placebo arm. In the trial-product estimand, weight loss ranged from minus 12.1 percent to minus 17 percent [3, 4]. HbA1c reductions of up to 2.2 percentage points were observed, with a high percentage of participants achieving normoglycemia (HbA1c less than 5.7 percent) [3].

Body composition: Dual-energy X-ray absorptiometry (DXA) assessments demonstrated that the majority of weight lost was fat mass. Lean mass decreased by approximately 9 to 12 percent in the obesity cohort and 7 to 10 percent in the obesity with diabetes cohort, compared with approximately 2 percent in placebo recipients [3]. The proportion of lean mass to total weight loss was consistent with the pattern observed with other GLP-1-based therapies.

Bone mineral density: No clinically significant changes in bone mineral density were observed across any treatment arm, a finding that distinguishes maridebart cafraglutide favorably from theoretical concerns about GIPR antagonism on osteoblast and osteoclast function [3].

Metabolic parameters: Clinically meaningful improvements were observed in blood pressure, triglycerides, and high-sensitivity C-reactive protein across dose levels [3, 4]. No significant increases in free fatty acids were observed.

The full Phase 2 results were presented at the American Diabetes Association 85th Scientific Sessions in June 2025 and published in the New England Journal of Medicine [3, 4].

7.3 Phase 3 MARITIME program

The Phase 3 MARITIME program initiated in 2025 comprises the following studies: MARITIME-1 (NCT06858878), a 72-week randomized, double-blind, placebo-controlled chronic weight management trial in adults with obesity or overweight without type 2 diabetes; MARITIME-2, a corresponding trial in adults with obesity or overweight with type 2 diabetes; and planned studies for atherosclerotic cardiovascular disease outcomes, heart failure outcomes, and obstructive sleep apnea [5, 6]. The Phase 3 dose selection was informed by the Phase 2 data, with dose-escalation protocols incorporated to mitigate gastrointestinal adverse events. Primary read-outs for the core weight management trials are expected in early 2027 [6].

8. Sourcing and Quality Verification

Maridebart cafraglutide is not commercially available as of the monograph date. The compound is accessible only through Amgen-sponsored clinical trials and through the investigational supply chain associated with those trials. It is not available from research chemical suppliers, compounding pharmacies, or generic pharmaceutical manufacturers.

As a recombinant biologic peptide-antibody conjugate, maridebart cafraglutide cannot be synthesized by conventional chemical methods and requires mammalian cell-culture expression systems, site-specific conjugation chemistry, and biologic-grade purification and characterization. The manufacturing complexity places it outside the scope of research-grade chemical sourcing that applies to small-molecule compounds.

Investigators seeking access to maridebart cafraglutide for research purposes should contact Amgen directly or apply through clinical trial enrollment at registered study sites. Independent quality verification of investigational drug supply follows institutional and regulatory frameworks (Good Manufacturing Practice certification, certificate of analysis from the sponsor, independent analytical confirmation by the study pharmacy).

For in vitro pharmacology studies requiring the isolated GLP-1R agonist peptide or the anti-GIPR antibody as individual components, research-grade surrogate molecules are available from specialty suppliers (MedChemExpress lists maridebart cafraglutide as a catalog item; availability and purity should be confirmed with the supplier) [22]. Investigators should confirm the identity, potency, and peptide-to-antibody ratio of any surrogate material before use in mechanistic studies.

9. Reconstitution and Handling

Maridebart cafraglutide is formulated by Amgen as a ready-to-use sterile liquid for subcutaneous injection, supplied in a prefilled single-use autoinjector device [5, 6]. The formulation does not require reconstitution by the end user.

Storage: Refrigerated storage at 2 to 8 degrees Celsius, protected from light, in the original carton. Do not freeze. The compound is a protein biologic and is subject to denaturation and aggregation at elevated temperatures and with freeze-thaw cycling.

Handling: Allow the autoinjector to reach room temperature (approximately 15 to 30 degrees Celsius) for approximately 30 minutes before injection. Do not use external heat sources to accelerate warming. Inspect visually for particulate matter and discoloration before administration; do not use if the solution is cloudy, discolored, or contains visible particles.

Injection sites: Subcutaneous injection into the abdomen (excluding a 2-inch radius around the navel), thigh, or upper arm. Rotate injection sites between doses.

Stability: Shelf-life data for the commercial formulation have not been publicly disclosed. Investigational supply is managed under Amgen's clinical trial drug management procedures with defined expiration dating.

For research applications involving the isolated compound (if available from specialty suppliers), standard biologic handling practices apply: aliquot to avoid freeze-thaw cycles, store lyophilized material at minus 20 or minus 80 degrees Celsius, reconstitute in the supplier-recommended buffer, and use reconstituted material within the supplier-specified timeframe.

10. Stack Interactions and Combinations

Maridebart cafraglutide interacts with several drug classes through its pharmacodynamic effects on glucose homeostasis, gastric motility, and appetite regulation. As an IgG-based biologic eliminated by catabolism rather than hepatic cytochrome P450 metabolism, conventional drug-drug pharmacokinetic interactions mediated by CYP inhibition or induction are not expected.

Insulin and insulin secretagogues: Concurrent use with insulin, sulfonylureas, or meglitinides carries a risk of additive hypoglycemia through the combination of GLP-1R-mediated glucose-dependent insulin secretion and the glucose-independent insulin secretion or exogenous insulin supply from the concurrent agent. Dose reduction of insulin or insulin secretagogues may be required when initiating maridebart cafraglutide, consistent with the standard practice for all GLP-1R agonists [13, 14].

Other GLP-1 receptor agonists: Concurrent use with another GLP-1R agonist (semaglutide, liraglutide, dulaglutide, exenatide) is pharmacologically redundant for the GLP-1R agonist component and may produce additive gastrointestinal adverse events. The combination has not been studied and is not recommended.

GIPR-targeting agents: Concurrent use with tirzepatide (a dual GLP-1R/GIPR agonist) would produce pharmacological conflict at the GIPR (agonism from tirzepatide, antagonism from maridebart cafraglutide). The combination has not been studied and is pharmacologically irrational.

Oral medications with absorption dependent on gastric motility: The GLP-1R-mediated delay in gastric emptying may reduce the rate of absorption of concurrently administered oral medications. This is a class effect of all GLP-1R agonists and is clinically relevant for oral medications with narrow therapeutic indices or time-dependent absorption (e.g., oral contraceptives, levothyroxine, warfarin) [13]. Patients should be advised to take critical oral medications at a consistent time relative to meals and to monitor for changes in drug effect when initiating or discontinuing maridebart cafraglutide.

Agents affecting bone metabolism: Theoretical interaction exists between GIPR antagonism and bone metabolism, given that GIPR is expressed on osteoblasts and osteoclasts and GIP stimulates bone formation. Concurrent use with bisphosphonates, denosumab, or teriparatide has not been studied. The Phase 2 data showing no clinically significant bone mineral density changes provide reassurance but do not exclude long-term effects [3].

QT-prolonging agents: No QT-prolongation signal has been identified for maridebart cafraglutide. Standard caution for novel investigational biologics applies pending thorough QT study data from the Phase 3 program.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events across Phase 1 and Phase 2 studies are gastrointestinal in origin, consistent with the GLP-1R agonist mechanism:

- Nausea (reported in 30 to 50 percent of active-treatment participants across dose groups, predominantly mild, most frequent with the first dose, diminishing with subsequent doses) [1, 3, 4]
- Vomiting (reported in 15 to 35 percent, predominantly mild and transient, resolving within 48 hours of dose administration) [1, 3, 4]
- Constipation (reported in 10 to 20 percent) [3, 4]
- Diarrhea (reported in 5 to 15 percent) [3, 4]
- Decreased appetite (reported as a pharmacodynamic effect rather than an adverse event in most participants) [3]

More than 90 percent of participants in active-treatment arms in the Phase 2 study experienced at least one adverse event, compared with 68 to 81 percent in the placebo arm [3, 4]. The higher overall adverse-event rate reflects the gastrointestinal events; non-gastrointestinal adverse-event rates were comparable between active treatment and placebo.

11.2 Dose-escalation mitigation

The Phase 2 study demonstrated that dose escalation from a lower starting dose (140 mg) to the target dose (420 mg) over 4 to 12 weeks substantially reduced the incidence and severity of gastrointestinal adverse events. The discontinuation rate due to gastrointestinal events was approximately 8 percent with dose escalation compared with 12 to 27 percent without dose escalation in the obesity cohort and 6 to 16 percent in the obesity with diabetes cohort [3, 4]. This finding informed the Phase 3 trial design, which incorporates mandatory dose escalation.

11.3 Injection-site reactions

Injection-site reactions (erythema, pruritus, swelling) were observed at rates comparable to placebo and were uniformly mild to moderate in severity [3]. No injection-site reactions led to study discontinuation.

11.4 Hypoglycemia

No treatment-related severe hypoglycemia was reported in Phase 1 or Phase 2 studies [1, 3]. The glucose-dependent mechanism of GLP-1R-mediated insulin secretion provides intrinsic protection against hypoglycemia in the absence of concurrent insulin or insulin secretagogue therapy.

11.5 Body composition safety

Lean body mass decreased by 9 to 12 percent in the obesity cohort and 7 to 10 percent in the obesity with diabetes cohort, compared with 2 percent in placebo recipients, over 52 weeks [3]. The proportion of weight lost as lean tissue (approximately 25 to 35 percent of total weight loss) is consistent with the pattern observed with other GLP-1-based therapies and with caloric restriction in general. No clinically significant changes in bone mineral density were observed in DXA assessments [3].

11.6 Cardiovascular safety

No cardiovascular safety signals (heart rate changes, QT prolongation, major adverse cardiovascular events) were identified in Phase 1 or Phase 2 studies [1, 3]. Dedicated cardiovascular outcomes studies are planned in the Phase 3 program.

11.7 Immunogenicity

Detailed immunogenicity data (incidence of anti-drug antibodies, neutralizing antibodies, and their impact on pharmacokinetics and efficacy) have not been fully reported in published literature as of monograph date. As an antibody-based biologic, maridebart cafraglutide carries theoretical immunogenicity risk. The fully human IgG2 scaffold is expected to have low immunogenic potential relative to chimeric or humanized antibodies. Immunogenicity assessments are incorporated into the Phase 3 program.

11.8 Pregnancy and lactation

Maridebart cafraglutide has not been studied in pregnant or lactating women. As an IgG2 molecule, the compound is expected to cross the placenta (particularly in the second and third trimesters, when FcRn-mediated transplacental IgG transport is active) and to be present in breast milk at low concentrations. Use in pregnancy and lactation is contraindicated pending reproductive toxicology data and risk-benefit assessment in the Phase 3 program.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five incretin-class obesity therapeutics against maridebart cafraglutide, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal approved or advanced-stage investigational incretin-based therapies for obesity.

12.1 Semaglutide (Wegovy)

Mechanism: Selective GLP-1 receptor agonist. Acylated GLP-1 analogue with an albumin-binding fatty acid side chain that extends half-life to approximately 7 days, supporting once-weekly subcutaneous injection [23].

Novelty: Low within the incretin class. Semaglutide is a second-generation GLP-1R agonist and represents an optimization of the liraglutide mechanism rather than a novel pharmacological concept.

Effect size: The STEP 1 trial reported mean weight loss of 14.9 percent at 68 weeks with semaglutide 2.4 mg weekly versus 2.4 percent with placebo in adults with obesity [23]. This established the benchmark for GLP-1R agonist monotherapy.

Promising potential: High. Semaglutide (Wegovy) is FDA-approved for chronic weight management (2021) and has received expanded cardiovascular outcomes indications based on the SELECT trial [24]. The compound is commercially established with demonstrated cardiovascular benefit.

Side-effect profile: Gastrointestinal adverse events (nausea 44 percent, diarrhea 30 percent, vomiting 24 percent in STEP 1) are the principal tolerability limitation [23]. Dose escalation over 16 weeks mitigates severity. Rare pancreatitis, gallbladder events, and medullary thyroid carcinoma risk (boxed warning, based on rodent C-cell tumor findings) are the serious safety considerations.

Overall validation: Very high. Semaglutide has the most extensive clinical evidence base of any anti-obesity biologic, with positive Phase 3 efficacy, cardiovascular outcomes, and real-world evidence data.

Comparison to maridebart cafraglutide: Semaglutide requires weekly dosing versus monthly for maridebart cafraglutide. The weight-loss magnitude is comparable at the highest doses (14.9 percent for semaglutide at 68 weeks versus 16 to 20 percent for maridebart cafraglutide at 52 weeks without plateau). Semaglutide lacks GIPR antagonism and the potential additive weight-loss mechanism. Semaglutide has the advantage of regulatory approval, cardiovascular outcomes data, and extensive real-world evidence; maridebart cafraglutide has the advantage of monthly dosing and the potential for greater long-term weight loss.

12.2 Tirzepatide (Zepbound)

Mechanism: Dual GLP-1R and GIPR agonist. A single acylated peptide that activates both GLP-1R (with GLP-1-like potency) and GIPR (with GIP-like potency), representing the first dual-incretin agonist approved for obesity [20].

Novelty: High. Tirzepatide introduced dual-incretin agonism as a clinical concept, demonstrating that GIPR agonism combined with GLP-1R agonism produces greater weight loss than GLP-1R agonism alone.

Effect size: The SURMOUNT-1 trial reported mean weight loss of 20.9 percent (tirzepatide 15 mg weekly) versus 3.1 percent (placebo) at 72 weeks in adults with obesity [20]. This established the highest weight-loss benchmark for any approved anti-obesity medication.

Promising potential: Very high. Tirzepatide (Zepbound) is FDA-approved for chronic weight management (2023) and (as Mounjaro) for type 2 diabetes (2022). Additional indications (heart failure, sleep apnea, MASH) are under investigation.

Side-effect profile: Gastrointestinal adverse events (nausea 24 to 33 percent, diarrhea 17 to 23 percent, vomiting 9 to 13 percent in SURMOUNT-1) [20]. Dose escalation over 20 weeks mitigates severity. The gastrointestinal adverse-event rate is generally comparable to or modestly lower than semaglutide at comparable weight-loss magnitudes.

Overall validation: Very high. Positive Phase 3 data across multiple indications, regulatory approval in two indications, and rapidly accumulating real-world evidence.

Comparison to maridebart cafraglutide: The two compounds represent opposing approaches to GIPR pharmacology (agonism versus antagonism). Weight-loss magnitude is comparable at the highest doses (20.9 percent for tirzepatide at 72 weeks versus up to 20 percent for maridebart cafraglutide at 52 weeks without plateau). Tirzepatide requires weekly dosing; maridebart cafraglutide requires monthly dosing. Tirzepatide has the advantage of regulatory approval and extensive clinical data; maridebart cafraglutide has the advantage of dosing convenience and the ongoing investigation of whether GIPR antagonism produces superior long-term outcomes.

12.3 Retatrutide (LY3437943)

Mechanism: Triple agonist at GLP-1R, GIPR, and the glucagon receptor (GCGR). The glucagon receptor agonism adds energy expenditure stimulation and hepatic lipid mobilization to the dual-incretin mechanisms [25].

Novelty: Very high. Retatrutide is the first triple-incretin agonist in advanced clinical development and represents a mechanistically distinct approach from both dual agonists and the GIPR-antagonist conjugate strategy.

Effect size: The Phase 2 trial reported mean weight loss of 24.2 percent at 48 weeks at the highest dose (12 mg weekly) versus 2.1 percent with placebo [25]. Phase 3 TRIUMPH-4 reported 28.7 percent weight loss at 68 weeks, the highest reported for any anti-obesity therapeutic in a controlled trial.

Promising potential: High. The compound is in Phase 3 development (Eli Lilly). Regulatory submission is anticipated pending Phase 3 readouts.

Side-effect profile: Gastrointestinal adverse events are the principal tolerability limitation (nausea, diarrhea, vomiting), with rates similar to or modestly higher than tirzepatide at comparable weight-loss magnitudes [25]. The glucagon receptor agonism raises theoretical concerns about hepatic glucose output and hyperglycemia, though clinical data have not demonstrated clinically significant hyperglycemia.

Overall validation: Moderate to high. Phase 2 and Phase 3 data are strongly positive but the compound is not yet approved.

Comparison to maridebart cafraglutide: Retatrutide achieves greater absolute weight loss (24 to 29 percent versus up to 20 percent) but requires weekly dosing and has a more complex three-receptor mechanism. Maridebart cafraglutide has the advantage of monthly dosing convenience and a mechanistically simpler dual-target profile. The two compounds are not directly comparable in mechanism because retatrutide includes glucagon receptor agonism that maridebart cafraglutide does not possess.

12.4 Survodutide (BI 456906)

Mechanism: Dual GLP-1R and glucagon receptor agonist. The glucagon receptor agonism differentiates survodutide from tirzepatide (which targets GIPR rather than GCGR) and from maridebart cafraglutide (which antagonizes GIPR) [26].

Novelty: Moderate to high. Dual GLP-1R/GCGR agonism is a distinct mechanistic approach that emphasizes energy expenditure and hepatic lipid metabolism alongside appetite suppression.

Effect size: Phase 2 data reported weight loss of approximately 13 to 19 percent at 46 to 48 weeks across dose groups. The compound has also demonstrated efficacy in metabolic dysfunction-associated steatohepatitis (MASH) with histological improvement [26].

Promising potential: Moderate to high. Phase 3 development (Boehringer Ingelheim) is ongoing for obesity and MASH.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea) are the principal tolerability limitation, with rates similar to other GLP-1R agonists. Heart rate increases have been observed, consistent with the glucagon receptor agonist component [26].

Overall validation: Moderate. Phase 2 data are positive; Phase 3 is ongoing but no registrational readout has been reported.

Comparison to maridebart cafraglutide: Survodutide and maridebart cafraglutide share the GLP-1R agonist component but differ in their second target (GCGR agonism for survodutide versus GIPR antagonism for maridebart cafraglutide).

Weight-loss magnitude is broadly comparable at Phase 2. Maridebart cafraglutide has the advantage of monthly dosing; survodutide requires weekly or more frequent injection. The MASH indication data for survodutide represent a therapeutic area not yet explored for maridebart cafraglutide.

12.5 Orforglipron (LY3502970)

Mechanism: Oral non-peptide GLP-1 receptor agonist. A small molecule that activates GLP-1R through a binding site distinct from the orthosteric peptide site, enabling oral bioavailability [27].

Novelty: High. Orforglipron represents the first orally bioavailable non-peptide GLP-1R agonist in advanced clinical development, overcoming the fundamental limitation of peptide-based GLP-1R agonists (requirement for injection).

Effect size: Phase 2 data reported mean weight loss of approximately 8 to 14.7 percent at 36 weeks at the highest studied doses [27]. This is lower than the injectable GLP-1R agonists and dual agonists at comparable timepoints.

Promising potential: High. Phase 3 development (Eli Lilly) is ongoing. The oral route of administration is a substantial convenience advantage over all injectable competitors.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea) at rates similar to injectable GLP-1R agonists. The oral route may produce more variable gastrointestinal tolerability owing to direct luminal exposure [27].

Overall validation: Moderate. Phase 2 data are positive; Phase 3 is ongoing.

Comparison to maridebart cafraglutide: The two compounds represent opposite ends of the convenience spectrum: orforglipron offers daily oral dosing (highest dosing frequency, no injection), while maridebart cafraglutide offers monthly subcutaneous injection (lowest dosing frequency, injection required). Weight-loss magnitude favors maridebart cafraglutide (up to 20 percent versus up to 14.7 percent at Phase 2). Orforglipron lacks the GIPR-antagonist mechanism. The choice between the approaches will depend on patient preference for oral versus injectable administration and on the final approved efficacy and safety profiles.

12.6 Comparator summary

The five comparators occupy distinct positions in the incretin-class anti-obesity therapeutic landscape. **Semaglutide** is the regulatory and commercial benchmark with extensive cardiovascular outcomes data and a well-characterized safety profile, but requires weekly injection and achieves lower weight loss than dual or multi-target agents. **Tirzepatide** represents the current efficacy benchmark among approved agents with 21 percent weight loss at 72 weeks and FDA approval in both obesity and type 2 diabetes, but requires weekly injection and employs GIPR agonism rather than antagonism. **Retatrutide** achieves the highest reported weight loss of any anti-obesity agent (29 percent at 68 weeks in Phase 3) through triple-receptor agonism but is not yet approved and requires weekly dosing. **Survodutide** offers an alternative dual-receptor approach (GLP-1R/GCGR) with particular promise in MASH but lower weight-loss magnitude than the GIPR-targeting agents. **Orforglipron** offers the convenience of oral dosing but with lower weight-loss efficacy than injectable alternatives.

Maridebart cafraglutide occupies a distinctive position: it is the only compound combining GLP-1R agonism with GIPR antagonism (rather than agonism), the only compound with once-monthly dosing enabled by the IgG2 antibody scaffold, and one of only two bispecific antibody-peptide conjugates in advanced obesity clinical development. The clinical weight-loss magnitude (up to 20 percent at 52 weeks without plateau) is competitive with the dual agonists and may improve with longer treatment duration as assessed in Phase 3 trials. The principal differentiation is the dosing interval: monthly injection versus weekly injection for all other advanced-stage injectable comparators, a potential adherence advantage in a therapeutic area where long-term treatment persistence is a recognized clinical challenge.

The GIPR agonism-versus-antagonism question remains the most consequential scientific distinction within this comparator set. Both tirzepatide (agonist) and maridebart cafraglutide (antagonist) achieve approximately 20 percent weight loss, and the hypothesis that chronic GIPR agonism functionally desensitizes the receptor (mimicking antagonism) provides one framework for understanding the convergent efficacy [19]. Whether the two approaches diverge in long-term outcomes, body-composition effects, or cardiovascular benefit is an open question that will be informed by the respective Phase 3 programs.

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