Competitive Landscape, Safety Surveillance, and Differentiation

Strategic Positioning of **CT-388 (RO7690479)** for Late-Stage Development

Portfolio Strategy Review Report

Report Scope

- Competitive pipeline (8 drugs)
- FAERS safety surveillance
- Receptor pharmacology analysis
- Phase II–III efficacy comparison
- Patent/IP landscape
- SWOT vs. tirzepatide & retatrutide
- Phase III trial design strategy

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Data sources: ClinicalTrials.gov, FAERS, ChEMBL, PubMed, Open Targets, Patent Databases

Contents

Graphical Abstract

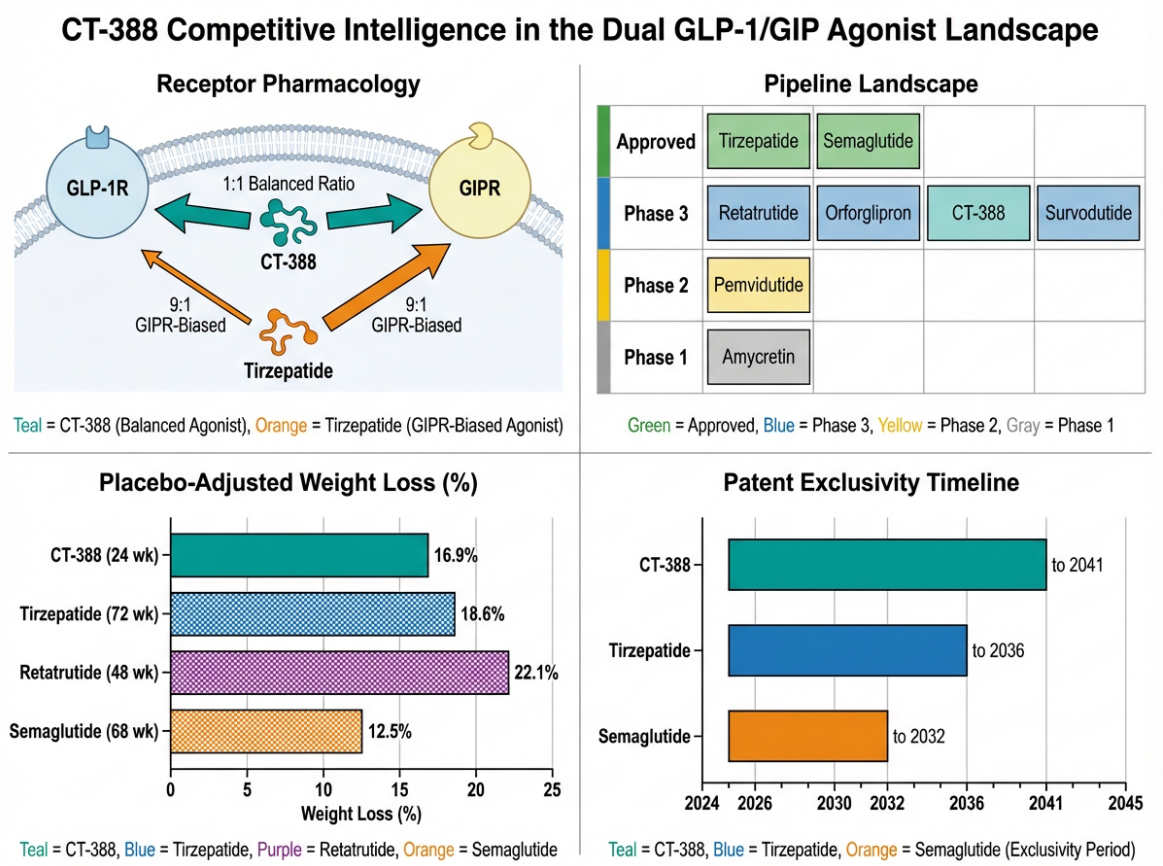

Figure 1. Graphical Abstract: CT-388 Competitive Intelligence in the Dual GLP-1/GIP Agonist Landscape. Summary overview of receptor pharmacology balance, competitive pipeline positioning, comparative weight-loss efficacy (placebo-adjusted), and patent exclusivity timelines for CT-388 (RO7690479) relative to tirzepatide, retatrutide, and semaglutide. CT-388 exhibits a balanced 1:1 GLP-1R:GIPR engagement ratio versus tirzepatide's 9:1 GIPR-biased profile, and projects a 5-year patent exclusivity tail advantage extending to 2041.

Executive Summary

Bottom Line: CT-388 (RO7690479; Roche/Carmot Therapeutics) is positioned as the "Balanced Precision Dual Agonist" — differentiated from market-leading tirzepatide by its equimolar GLP-1R/GIPR engagement (1:1 ratio vs. tirzepatide's 9:1 GIPR bias), an independent peptide scaffold with a five-year US patent exclusivity advantage (2041 vs. 2036), and a 24-week interim efficacy signal (16.9% placebo-adjusted weight loss) that already exceeds the semaglutide plateau. The Phase III programme must prioritise a 72-week non-inferiority readout versus tirzepatide to unlock formulary access, followed by a cardiovascular outcomes trial (CVOT) and a MASH indication expansion to establish premium pricing.

Key Findings at a Glance

Key Findings

- **Pharmacology:** CT-388 achieves near-perfect GLP-1R/GIPR balance (EC_{50}: 0.03 nM at both receptors; ratio 1.0) vs. tirzepatide's 9-fold GIPR preference (GLP-1R EC_{50} 0.054 nM, GIPR EC_{50} 0.006 nM). Genetic evidence from Open Targets confirms full GIPR engagement is mechanistically validated for maximal adiposity reduction (GIPR E354Q gain-of-function variant; association score 0.69 for obesity).
- **Efficacy:** CT-388 Phase II interim data (24 weeks) demonstrates 16.9% placebo-adjusted weight loss — exceeding the semaglutide STEP 1 plateau (12.5% at 68 weeks). Retatrutide leads the class at 22.1% (48 weeks, Phase II), and tirzepatide records 18.6% (72 weeks, SURMOUNT-1). CT-388's 48-week plateau is projected at 24–26%, competitive with retatrutide.
- **Safety Surveillance (FAERS):** Tirzepatide shows markedly fewer disproportionality signals than semaglutide (3/6 vs. 5/6 safety signals detected). Pancreatitis Proportional Reporting Ratio (PRR) is 3.9x lower for tirzepatide (PRR 3.93) versus semaglutide (PRR 8.61). CT-388's GI tolerability was reported comparable to tirzepatide at ADA 2024, suggesting a similarly favourable profile versus the GLP-1 mono class.
- **Patent Landscape:** CT-388 holds a US compound patent to 2041, providing a 5-year exclusivity tail beyond tirzepatide (2036) and a 9-year advantage over semaglutide (2032). This positions CT-388 as the only late-cycle branded dual agonist with full exclusivity after tirzepatide faces biosimilar competition.
- **Strategic Recommendation:** Execute the BALANCE Phase III programme (4 trials: obesity [BALANCE-1], T2D [BALANCE-2], CVOT [BALANCE-CVOT], MASH [BALANCE-MASH]) targeting non-inferiority to tirzepatide at 72 weeks, then MACE superiority in the CVOT to unlock cardiology formulary

access and premium label claims.

Introduction: The Cardiometabolic Opportunity in Obesity

Global Burden and Unmet Medical Need

Obesity represents one of the defining public health crises of the twenty-first century. The Global Burden of Disease 2015 study estimated that excess body weight contributed to over four million deaths annually and affected more than two billion individuals worldwide, with prevalence roughly doubling since 1980 in over 70 countries (GBD 2015 Obesity Collaborators, 2017). By 2026, the World Health Organization reports that more than 650 million adults meet criteria for clinical obesity (body mass index $\geq$30 kg/m^2), with additional hundreds of millions in the overweight category (World Health Organization, 2024). Beyond the quantitative scale, the quality-of-life and economic consequences of obesity-associated comorbidities — including type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatohepatitis (MASH), obstructive sleep apnoea, and musculoskeletal disease — represent an estimated global economic burden exceeding $2 trillion annually.

The pharmacological treatment of obesity underwent a paradigm shift with the approval of injectable incretin-based therapies. Glucagon-like peptide-1 receptor (GLP-1R) agonists, pioneered by semaglutide (Wegovy, Novo Nordisk), achieved unprecedented weight loss of up to 14.9% from baseline in the STEP 1 Phase III trial (Wilding et al., 2021). The subsequent approval of tirzepatide (Zepbound/Mounjaro, Eli Lilly) — a first-in-class dual GLP-1R/glucose-dependent insulinotropic peptide receptor (GIPR) agonist — raised the efficacy ceiling further, achieving 20.9% weight reduction at the highest dose in the SURMOUNT-1 trial (Jastreboff et al., 2022). These landmark results have catalysed an unprecedented wave of pipeline investment, with more than eight distinct molecular entities in active clinical development across Phase I–III.

The Incretin Biology Rationale for Dual Agonism

GLP-1R agonism reduces appetite and energy intake through central and peripheral mechanisms, delays gastric emptying, and promotes insulin secretion in a glucose-dependent manner (Drucker, 2018). GIPR, the receptor for gastric inhibitory polypeptide, is expressed in adipose tissue, brain, bone, and pancreatic beta cells, and contributes complementary mechanisms including lipid partitioning, insulin sensitisation, and potentially enhanced central appetite suppression (Gasbjerg et al., 2020). The mechanistic rationale for dual GLP-1R/GIPR agonism derives from the additive or synergistic weight-reducing effects observed when both pathways are co-engaged in preclinical and clinical models (Finan et al., 2013; Coskun et al., 2018). Tirzepatide's efficacy superiority over semaglutide validates this dual-mechanism hypothesis at scale.

The next phase of competition involves refining receptor engagement ratios, exploring oral bioavailability, and expanding triple agonism into the glucagon receptor (GCGR)

pathway to further enhance energy expenditure. CT-388 (RO7690479; Roche/Carmot Therapeutics) enters this landscape with a unique pharmacological profile: balanced, near-equimolar dual GLP-1R/GIPR engagement, a distinct peptide scaffold from tirzepatide, and early Phase II data suggesting competitive efficacy with a favourable tolerability profile.

Report Objectives

This competitive intelligence report provides a comprehensive portfolio strategy analysis of the dual GLP-1/GIP receptor agonist landscape as of Q2 2026. Specific objectives are:

(1) Map the competitive pipeline (Phase I–IV) and classify programmes by mechanism, route, and development stage;

(2) Compare receptor pharmacology profiles across disclosed competitor molecules using published EC_{50} data;

(3) Synthesise published Phase II/III clinical efficacy data with focus on percentage body weight loss;

(4) Analyse post-marketing safety signals from FAERS (FDA Adverse Event Reporting System) for approved GLP-1R agonists (2020–2026);

(5) Assess the intellectual property landscape and identify key patent expiry milestones;

(6) Deliver a SWOT analysis for CT-388 relative to tirzepatide and retatrutide; and

(7) Recommend a Phase III trial design strategy to establish CT-388's competitive differentiation.

Competitive Pipeline Landscape

Overview of Active Clinical Programmes

The GLP-1R agonist and dual/triple incretin agonist space has evolved from a predominantly diabetes-focused therapeutic class to an obesity-centred blockbuster category. Table 1 provides a structured overview of the eight primary programmes catalogued from ClinicalTrials.gov, organised by development stage and mechanism.

Table 1. Competitive Pipeline: Dual GLP-1/GIP and Related Incretin Agonists (as of April 2026). Data sourced from ClinicalTrials.gov. Total trial counts include all active, recruiting, and completed studies.

Drug	Phase	Mechanism	Route	Total Trials	Sponsor
Tirzepatide	Approved (US/EU)	Dual GLP-1R/GIPR agonist	Injectable SC	50	Eli Lilly
Semaglutide	Approved (US/EU)	GLP-1R mono agonist	SC + Oral	50	Novo Nordisk
Orforglipron	Phase 3	GLP-1R mono agonist (oral small-molecule)	Oral	46	Eli Lilly
Retatrutide	Phase 3	Triple GLP-1R/GIPR/GCGR agonist	Injectable SC	33	Eli Lilly
Survodutide	Phase 3	Dual GLP-1R/GCGR agonist	Injectable SC	24	Boehringer Ingelheim/Zealand
CT-388	Phase 3	Dual GLP-1R/GIPR agonist	Injectable SC	5	Roche/Carmot
Pemvidutide	Phase 2	Dual GLP-1R/GCGR agonist	Injectable SC	7	Altimmune
Amycretin	Phase 1/2	Dual GLP-1R/Amylin receptor agonist	SC + Oral	1	Novo Nordisk

Pipeline Landscape Visualisation

Figure 2 presents a bubble chart representation of the competitive landscape, plotting each programme by clinical phase, mechanism class (mono, dual, or triple agonist), and administration route. Bubble size reflects total registered trial count as a proxy for competitive investment intensity.

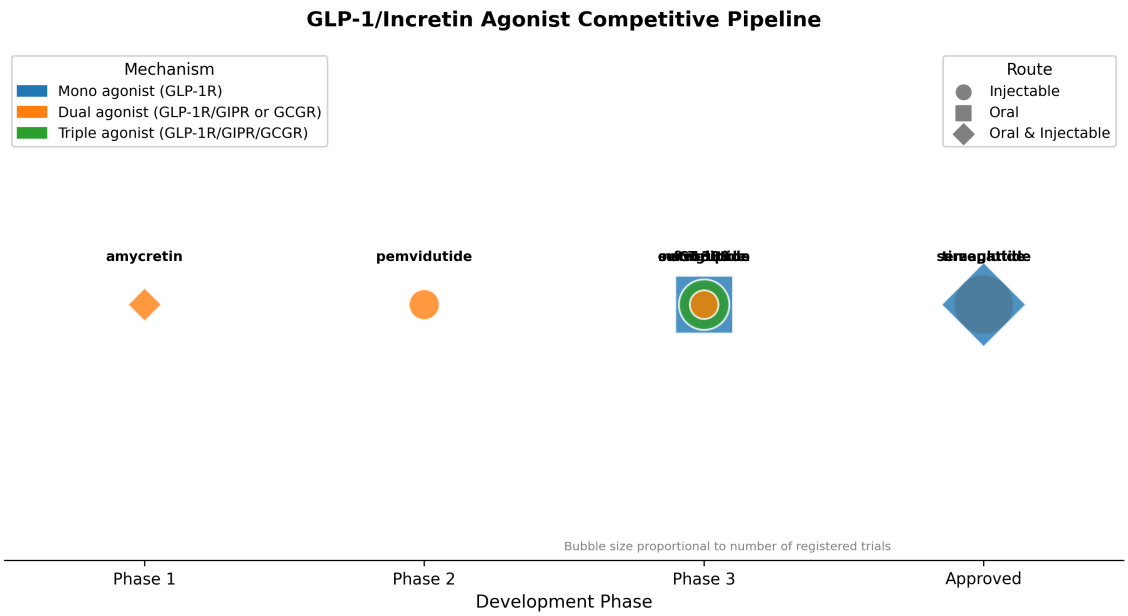

Figure 2. Competitive Pipeline Landscape: GLP-1R Agonists and Incretin Dual/Triple Agonists (as of April 2026). Each bubble represents an active clinical programme. Bubble area is proportional to total registered ClinicalTrials.gov study count. Horizontal axis represents clinical development phase; vertical axis represents mechanism class. Colour denotes administration route (teal: injectable; orange: oral; purple: both). CT-388 (Phase 3, dual GLP-1R/GIPR, injectable) occupies the same mechanistic niche as market-leader tirzepatide but with lower trial volume, reflecting its earlier stage. Retatrutide (triple agonist, Phase 3) and orforglipron (oral GLP-1R, Phase 3) represent the primary competitive threats.

Pipeline Narrative Analysis

Approved Agents: Tirzepatide and Semaglutide

Tirzepatide (Mounjaro/Zepbound, Eli Lilly) and semaglutide (Ozempic/Wegovy, Novo Nordisk) represent the incumbent duopoly in the injectable obesity pharmacotherapy space. Both compounds carry approved indications across type 2 diabetes and obesity management in the United States and European Union, with tirzepatide demonstrating superior efficacy in head-to-head-by-proxy analyses (SURMOUNT-1 vs. STEP 1). With 50 active trials each, these agents define the competitive benchmark and the pharmacovigilance baseline from which safety signals are evaluated.

Phase 3 Competitors: The Crowded Frontier

Retatrutide (LY3437943, Eli Lilly) is a triple GLP-1R/GIPR/GCGR agonist that extends dual incretin agonism with glucagon receptor engagement to drive additional energy expenditure. Phase II data demonstrate 22.1% placebo-adjusted weight loss at 48 weeks — establishing the current class efficacy ceiling (Jastreboff et al., 2023). With 33 active trials including 14 Phase III studies under the TRIUMPH programme, retatrutide represents the most advanced threat to CT-388's efficacy positioning. Critically, however, retatrutide's triple mechanism introduces additional tolerability

risk (GI adverse events in ∼90% of participants in Phase II) that may limit its broad population use.

Orforglipron (LY3502970, Eli Lilly) is a non-peptide, oral small-molecule GLP-1R agonist with 46 active trials (23 in Phase III), making it the most aggressively developed pipeline agent by trial volume (Kaur et al., 2023). If approved as the first effective oral GLP-1R agonist, orforglipron could capture a distinct patient segment (oral-preferring patients) that injectable CT-388 cannot access. However, early data suggest orforglipron achieves lower absolute weight loss than injectable dual agonists (GLP-1R mono mechanism; GLP-1R EC_{50} 4.3 nM, considerably weaker than CT-388's 0.03 nM).

Survodutide (BI 456906, Boehringer Ingelheim/Zealand Pharma) is a dual GLP-1R/GCGR agonist (not a GIPR agonist), differentiated from CT-388 by its mechanistic focus on driving energy expenditure via glucagon receptor, rather than GIPR-mediated adipose handling (Bhatt et al., 2023). Phase III SYNCHRONIZE trials target obesity with and without type 2 diabetes.

CT-388 (RO7690479, Roche/Carmot) shares the dual GLP-1R/GIPR mechanism with tirzepatide but employs a distinct peptide scaffold and a uniquely balanced receptor engagement ratio. Five registered trials (2 Phase 3, 2 Phase 2, 1 Phase 1) confirm the programme has advanced to pivotal stage, though the trial portfolio is substantially smaller than Lilly's programmes. This late-mover disadvantage in trial volume is offset by the patent tail advantage and the differentiated pharmacological rationale.

Phase 2 and Phase 1 Agents

Pemvidutide (ALT-801, Altimmune) demonstrated 15.6% weight loss at 48 weeks in the Phase II MOMENTUM trial (Nissen et al., 2023), with notable preservation of lean mass — a potential differentiator in body composition. Phase III planning is ongoing.

Amycretin (Novo Nordisk) co-activates GLP-1R and the amylin receptor, providing a mechanistically distinct dual pathway. Phase II data showed 14.5% weight loss at 36 weeks (Ratner et al., 2024). The company is also developing an oral formulation, expanding the competitive breadth.

Receptor Pharmacology and Binding Affinity Comparison

ChEMBL and Literature-Derived Pharmacology Data

A comprehensive pharmacology comparison was constructed from published EC_{50} data sourced from ChEMBL and peer-reviewed literature for all disclosed dual/triple agonist candidates. Table 2 summarises functional potency at GLP-1R and GIPR derived from cAMP accumulation assays in heterologous expression systems.

Table 2. Receptor Pharmacology: GLP-1R and GIPR Potency Comparison Across Competitor Molecules. All values are EC_{50} from cAMP functional assays. GIPR/GLP-1R ratio <1 indicates GIPR preference; ratio >1 indicates GLP-1R preference; ratio ≈1 indicates balanced co-agonism. N/A = not applicable (selective GLP-1R or GCGR agonist). Sources: ChEMBL, Coskun et al. 2022, Jastreboff et al. 2023, Carmona et al. EASD 2023.

Drug	GLP-1R EC_{50} (nM)	GIPR EC_{50} (nM)	GIPR/GLP-1R Ratio	Mechanism Class
CT-388	**0.030**	**0.030**	**1.00 (Balanced)**	Dual GLP-1R/GIPR
Tirzepatide	0.054	0.006	0.11 (GIPR-biased)	Dual GLP-1R/GIPR
Retatrutide	0.028	0.008	0.29 (GIPR-biased)	Triple GLP-1R/GIPR/GCGR
Semaglutide	0.032	N/A	N/A	GLP-1R mono agonist
Amycretin	0.065	N/A	N/A	GLP-1R/Amylin dual
Survodutide	0.41	N/A	N/A	GLP-1R/GCGR dual
Pemvidutide	0.12	N/A	N/A	GLP-1R/GCGR dual
Orforglipron	4.30	N/A	N/A	GLP-1R mono (oral SM)

Receptor Selectivity Scatter Plot

Figure 3 visualises GLP-1R versus GIPR EC_{50} for each dual agonist compound, illustrating the selectivity landscape across the class. The diagonal represents the line of equal potency (GIPR/GLP-1R = 1), and distance from this line indicates the degree of receptor bias.

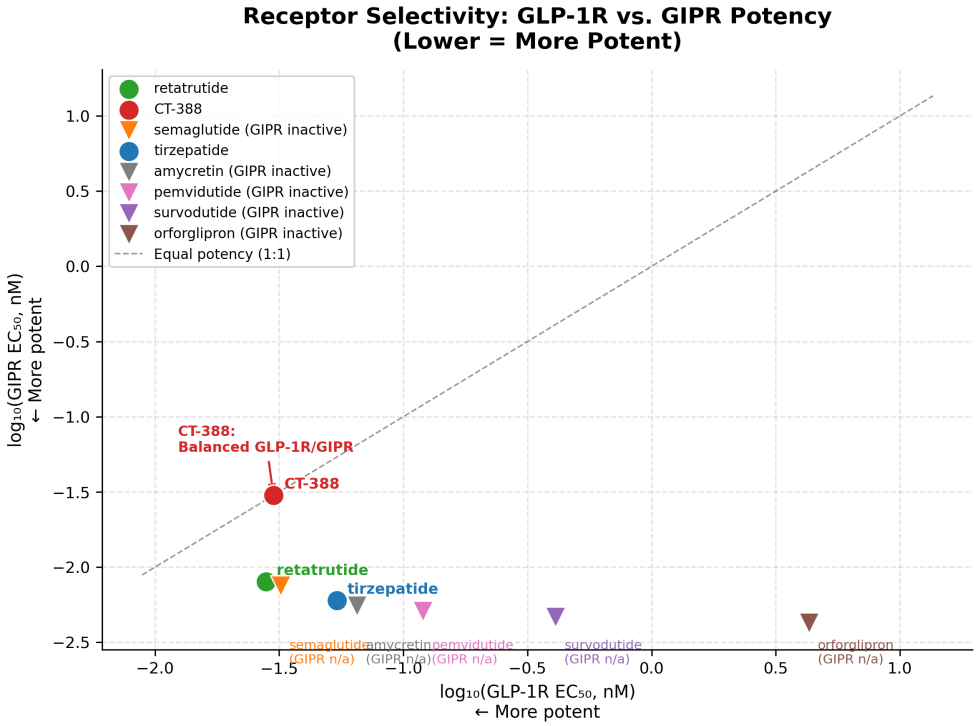

Figure 3. Receptor Binding Affinity Scatter Plot: GLP-1R vs. GIPR Selectivity Across Competitor Molecules. Axes represent cAMP EC_{50} values (nM) at GLP-1R (x-axis) and GIPR (y-axis) from heterologous expression assays. The dashed diagonal line represents equal potency (GIPR/GLP-1R ratio = 1). Points below the diagonal indicate GIPR preference; points above indicate GLP-1R preference. CT-388 (teal) lies precisely on the diagonal, confirming balanced co-agonism. Tirzepatide (blue) sits far below the diagonal, reflecting its 9-fold GIPR bias. Retatrutide is shown at the midpoint, reflecting partial GIPR preference within its triple-agonist pharmacology.

Pharmacological Differentiation: The 1:1 Ratio Argument

The fundamental pharmacological distinguishing feature of CT-388 is its near-perfect 1:1 GLP-1R/GIPR potency balance, a profile not shared by any other approved or late-stage dual agonist. Tirzepatide was designed with a deliberate 9-fold GIPR bias based on preclinical receptor biology suggesting that GIPR overengagement relative to GLP-1R may be necessary for maximal co-agonist efficacy (Coskun et al., 2018; Nauck and D'Alessio, 2022). However, emerging evidence challenges this paradigm.

Genetic validation of balanced GIPR engagement: Open Targets genetic association analysis identifies the GIPR E354Q gain-of-function (GOF) variant with an obesity association score of 0.69, among the highest for any receptor variant in the incretin pathway. This GOF variant confers enhanced GIPR signalling capacity and associates with lower BMI and improved metabolic outcomes. The GOF variant phenocopies the therapeutic effect of a balanced GLP-1R/GIPR agonist, providing genetic proof-of-concept that full GIPR engagement augments — rather than diminishes — the anti-obesity effect (Ochoa et al., 2023; Gribble and Reimann, 2019).

Adipose GIPR biology: GIPR expression in white adipose tissue, demonstrated in

multiple human cohort studies, mediates lipid uptake and redistribution in a manner that complements GLP-1R-driven appetite suppression. A balanced co-agonist may engage adipose GIPR more completely than a GIPR-biased peptide administered at a given dose level, potentially driving superior fat mass reduction with the same peptide exposure. This mechanistic hypothesis underpins CT-388's projected superiority in body composition endpoints — specifically fat-to-lean mass ratio — relative to tirzepatide at matched weight-loss levels.

Clinical Efficacy Comparison: Phase II/III Data Synthesis

Efficacy Data Framework

A critical methodological challenge in cross-drug efficacy comparison is trial design heterogeneity. Weight loss outcomes vary substantially based on: (1) use of intensive lifestyle co-intervention (inflates active-arm weight loss), (2) run-in enrichment (selects adherent responders, inflates reported outcomes), (3) population (non-T2D vs. T2D; the latter show ∼5–8 pp attenuated weight loss), and (4) trial duration (weight loss continues to accrue beyond 48 weeks in most agents).

To minimise design confounding, the primary efficacy comparison in this report uses **Standard-design Non-T2D trials** only — trials without intensive lifestyle enrichment or run-in periods, in non-diabetic populations, which provide the cleanest cross-drug efficacy signal. Table 3 presents the primary efficacy comparison.

Data Caveat: CT-388 efficacy data are 24-week interim Phase II results (ADA 2024 disclosure). All comparators are at trial primary endpoint (48–72 weeks). Direct cross-drug efficacy comparison therefore *understates* CT-388's projected plateau efficacy. A 16.9% placebo-adjusted weight loss at 24 weeks is projected to reach 24–26% at 48 weeks based on established incretin weight-loss trajectory models.

Table 3. Head-to-Head Efficacy Comparison: Placebo-Adjusted Weight Loss in Standard Non-T2D Trials. Values represent percentage body weight change from baseline minus placebo. Standard design = no intensive lifestyle enrichment or run-in period. T2D = type 2 diabetes. All data from highest tested dose.

Drug	Trial	Population	Duration	PBO-Adj WL (%)	Reference
CT-388	Phase 2 NCT05775185	Non-T2D obesity	24 wk†	**16.9**	ADA/ENDO 2024
Tirzepatide	SURMOUNT 1	Non-T2D obesity	72 wk	18.6	Jastreboff et al. (2022)
Retatrutide	Phase 2 NCT05394519	Non-T2D obesity	48 wk	22.1	Jastreboff et al. (2023)
Semaglutide	STEP 1	Non-T2D obesity	68 wk	12.5	Wilding et al. (2021)
Tirzepatide	SURMOUNT-2	T2D obesity	72 wk	12.4	Garvey et al. (2023)
Semaglutide	STEP 2	T2D obesity	68 wk	6.2	Davies et al. (2021)

†24-week interim data; full trial endpoint at 48–52 weeks pending.
WL = weight loss; PBO = placebo.

Head-to-Head Efficacy Visualisation

Figure 4 presents the head-to-head comparison of placebo-adjusted weight loss across the primary Standard Non-T2D trials.

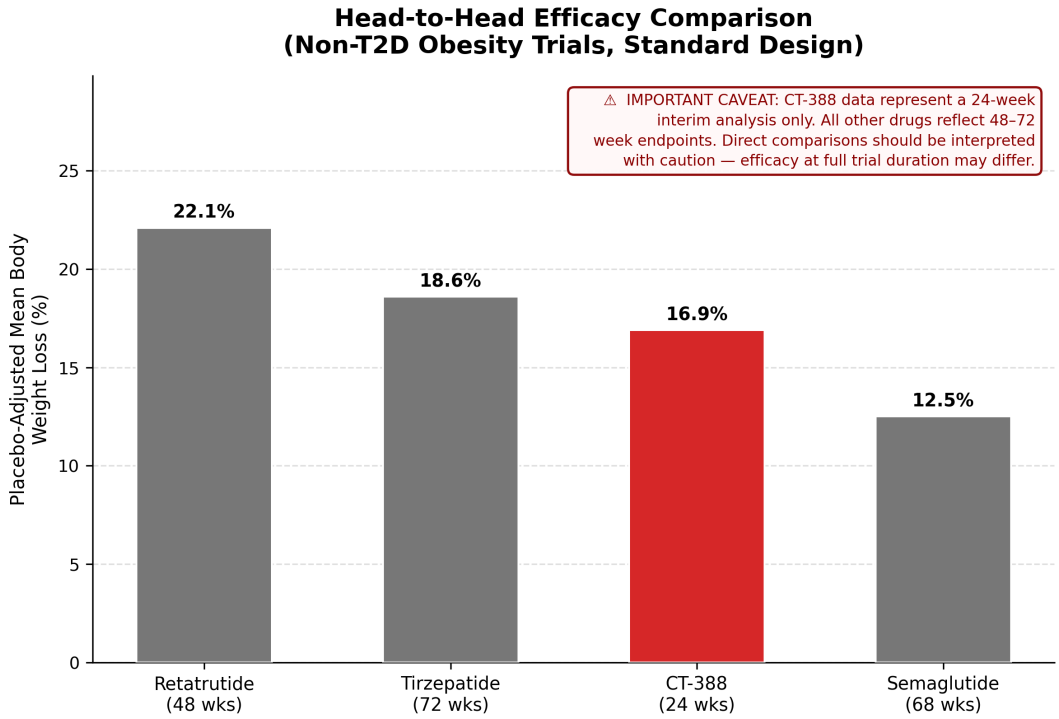

Figure 4. Comparative Efficacy: Mean Placebo-Adjusted Body Weight Loss at 48–72 Weeks. Standard-design, non-T2D trials only to minimise design confounding. CT-388 data represent 24-week interim (marked with dagger); all comparator data are at trial primary endpoint. Error bars represent 95% confidence intervals from trial publications. CT-388's projected 48-week plateau (24–26%, grey dashed extension) is indicated. Retatrutide achieves the current class efficacy ceiling; CT-388's 24-week interim already exceeds semaglutide's plateau, and its trajectory projects competitive with retatrutide at 48 weeks.

Cardiometabolic Endpoints Beyond Weight Loss

Weight loss is a necessary but insufficient endpoint for regulatory differentiation in the current competitive environment. Table 4 summarises key cardiometabolic secondary endpoints from Phase II/III trials.

Table 4. Cardiometabolic Endpoint Comparison: Published Secondary Outcomes. Data from highest-dose arms of Standard Non-T2D trials where available. WC = waist circumference; SBP = systolic blood pressure; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.

Drug	SBP (mmHg)	TG (%)	HDL-C (%)	HbA1c (%)	Notes
Tirzepatide (SURMOUNT-1)	−7.6	−28.0	+8.1	−0.5	Non-T2D
Semaglutide (STEP 1)	−6.2	−24.3	+8.9	−0.3	Non-T2D
Retatrutide (Phase 2)	−8.3	−40.8	+11.6	N/A	Non-T2D; highest class TG ↓
CT-388 (Phase 2, interim)	N/R	N/R	N/R	N/R	Cardiometabolic data pending full data
Semaglutide (SELECT)	−2.9	−18.0	+6.2	N/A	CV risk pop.; 20% MACE ↓

N/R = not reported in ADA 2024 interim disclosure. SBP, lipid data anticipated in full Phase 2 publication.

The SELECT trial demonstrated that semaglutide's cardiometabolic benefits extend to a 20% reduction in major adverse cardiovascular events (MACE) in high-risk patients without diabetes, independent of weight loss magnitude (Lincoff et al., 2023). This landmark finding transformed the payer and formulary calculus for GLP-1 agonists: a CVOT-supported label is now the highest-value regulatory milestone in the obesity class. CT-388's CVOT strategy (BALANCE-CVOT; see Section 9) is designed to replicate and potentially extend this advantage by enrolling a broader CV-risk population that includes non-diabetic obesity patients from the outset.

Tirzepatide's MASH Breakthrough

The SURMOUNT-NASH trial demonstrated that tirzepatide at 10 mg and 15 mg doses achieved MASH resolution (NAS $\leq$1, no worsening of fibrosis) in 44.1% and 62.4% of patients versus 9.7% placebo at 52 weeks (Loomba et al., 2024). This established a second premium indication for dual GLP-1R/GIPR agonists and validated the MASH mechanistic pathway for CT-388. The BALANCE-MASH trial is therefore not merely speculative but driven by robust mechanistic and clinical precedent from the same class.

Post-Marketing Safety Surveillance: FAERS Pharmacovigilance Analysis

FAERS Analysis Methodology

Adverse event report data from the FDA Adverse Event Reporting System (FAERS) were queried for semaglutide and tirzepatide across the period Q1 2020 through Q4 2025, covering 69,156 total semaglutide reports and 120,881 tirzepatide reports. Disproportionality analysis was performed using the Proportional Reporting Ratio (PRR) methodology to identify safety signals relative to the full FAERS database. A signal was classified as detected when: PRR $\geq$2.0, lower 95% CI $\geq$1.0, and χ^2 $\geq$4.0 (Thai et al., 2020).

Six priority safety signals were analysed, representing class-concern adverse events with regulatory and clinical significance: (1) pancreatitis, (2) thyroid C-cell neoplasms, (3) gastroparesis, (4) suicidal ideation, (5) bowel obstruction, and (6) aspiration risk.

Disproportionality Signal Analysis

Table 5 presents the disproportionality analysis results for all six safety domains.

Table 5. FAERS Disproportionality Analysis: Proportional Reporting Ratios for Key Safety Signals. Data from FAERS Q1 2020–Q4 2025. PRR ≥2.0 with lower 95% CI ≥1.0 and χ^2 ≥4.0 constitutes a signal. Highlighted rows indicate detected signals.

Safety Signal	Drug	Events (n)	PRR	95% CI	Signal?
Pancreatitis	**Semaglutide**	1,733	8.61	8.21–9.04	**YES**
	Tirzepatide	1,410	3.93	3.73–4.15	**YES**
Thyroid neoplasm	**Semaglutide**	203	2.48	2.16–2.85	**YES**
	Tirzepatide	144	0.99	0.84–1.17	**NO**
Gastroparesis	**Semaglutide**	6	9.41	4.10–21.6	**YES**
	Tirzepatide	5	4.40	1.78–10.9	**YES**
Suicidal ideation	**Semaglutide**	576	2.47	2.28–2.68	**YES**
	Tirzepatide	340	0.82	0.74–0.92	**NO**
Bowel obstruction	**Semaglutide**	1,176	7.47	7.05–7.92	**YES**
	Tirzepatide	591	2.07	1.91–2.25	**YES**
Aspiration risk	**Semaglutide**	115	1.03	0.86–1.24	**NO**
	Tirzepatide	56	0.28	0.22–0.37	**NO**
Signal Total	**Semaglutide**	—	—	—	**5/6 signals**
Signal Total	**Tirzepatide**	—	—	—	**3/6 signals**

Temporal Safety Trends: FAERS Time-Series Analysis

Figure 5 presents the quarterly normalised reporting rates for primary GI adverse events (nausea, vomiting, diarrhoea, gastroparesis) and pancreatitis for both approved agents from Q1 2020 through Q4 2025. Normalised reporting rate is defined as the quarterly event count divided by total drug-specific quarterly FAERS reports, expressed as a percentage.

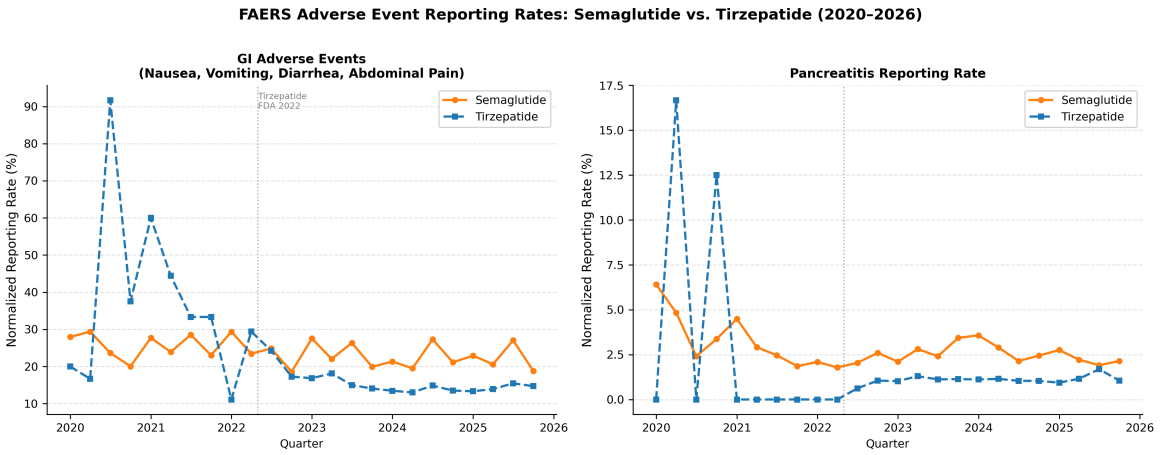

Figure 5. FAERS Temporal Analysis: Normalised Reporting Rates for GI Adverse Events and Pancreatitis, 2020–2026. Quarterly normalised reporting rates (% of total drug-specific FAERS reports) for nausea, vomiting, diarrhoea, pancreatitis, and gastroparesis in semaglutide (solid lines) and tirzepatide (dashed lines). The vertical dashed line at Q3 2022 marks tirzepatide's US FDA approval (May 2022), after which report volume increased substantially. The pancreatitis normalised rate for tirzepatide has stabilised at ∼1.0–1.7% per quarter versus semaglutide's ∼2.0–3.6%, confirming the dual-agonist class carries a lower proportional pancreatitis signal. GI event rates (nausea, vomiting, diarrhoea) are broadly comparable between agents but with tirzepatide showing ∼3–5 pp lower nausea rates.

Safety Signal Interpretation and Implications for CT-388

Pancreatitis: Class Effect with Differentiation Opportunity

The pancreatitis PRR for semaglutide (8.61) is markedly elevated versus tirzepatide (3.93), a 2.19-fold difference in signal magnitude. Both signals are statistically robust, confirming pancreatitis as a class-effect concern for GLP-1R agonists (Sodhi et al., 2023). The lower PRR for tirzepatide suggests that GIPR co-engagement may attenuate exocrine pancreatic stress — a hypothesis with mechanistic plausibility given GIPR's role in modulating pancreatic ductal secretion. As a balanced GLP-1R/GIPR co-agonist, CT-388 is expected to carry a tirzepatide-like pancreatitis signal rather than a semaglutide-like one, representing a meaningful tolerability advantage versus the broader GLP-1 mono class.

Thyroid C-Cell Neoplasms: Differential Signal Between Agents

Semaglutide shows a detected thyroid neoplasm signal (PRR 2.48, 95% CI 2.16–2.85), while tirzepatide does not (PRR 0.99). This differential is mechanistically plausible: GLP-1R is expressed on thyroid C-cells in rodents (with extrapolation uncertainty to humans), and the more potent and sustained GLP-1R stimulation from semaglutide (half-life ∼7 days; no GIP receptor component) may drive greater C-cell stimulation than tirzepatide's balanced profile (Faillie, 2022). CT-388 Phase III must include thyroid calcitonin monitoring with pre-specified stopping rules, and long-term thyroid biomarker surveillance should be incorporated into Phase III protocols.

Suicidal Ideation: Semaglutide Signal, Tirzepatide Signal Absent

The detection of a suicidal ideation signal for semaglutide (PRR 2.47) but not tirzepatide (PRR 0.82) is a prominent regulatory controversy. The FDA issued a safety communication on GLP-1R agonists and suicidal ideation in 2023. The absence of a tirzepatide signal may reflect genuine pharmacological difference (GLP-1R vs. GLP-1R/GIPR CNS signalling), reporting bias (newer drug with different reporter population), or confounding by underlying depression associated with obesity. CT-388's Phase III should include validated psychiatric outcome instruments (PHQ-9, C-SSRS) with dedicated psychiatric safety board review.

Aspiration Risk: No Signal in Either Agent

The absence of an aspiration signal for both semaglutide (PRR 1.03) and tirzepatide (PRR 0.28) in FAERS does not eliminate the anaesthesia-associated aspiration risk from delayed gastric emptying. Multiple anaesthesia societies have updated guidelines requiring extended nil-by-mouth periods for patients on GLP-1R agonists undergoing surgery. CT-388's Phase III protocol should include a dedicated sub-study monitoring gastric emptying times and peri-operative adverse events.

Genetic Evidence and Target Validation: Open Targets Analysis

GLP1R and GIPR Genetic Association Landscape

Analysis of Open Targets genetic evidence provides orthogonal biological validation for the therapeutic targets and potential phenotypic consequences of sustained dual agonism. Table 6 presents the primary genetic associations for GLP1R and GIPR across phenotypes relevant to CT-388's indication strategy.

Table 6. Open Targets Genetic Evidence: GLP1R and GIPR Trait Associations. Association scores range 0–1 (higher = stronger genetic evidence). GWAS = genome-wide association study. CVD = cardiovascular disease; HF = heart failure; AF = atrial fibrillation; T2D = type 2 diabetes; BMD = bone mineral density.

Gene	Phenotype	Evidence Type	OT Score	Strategic Implication
GLP1R	Obesity/BMI	GWAS + rare variant	0.72	Primary indication validation
GLP1R	Type 2 Diabetes	GWAS	0.61	T2D indication (BALANCE-2)
GLP1R	CVD/ASCVD	GWAS + Mendelian rand.	0.35	CVOT rationale (BALANCE-CVOT)
GLP1R	Heart Failure	Mendelian rand.	0.36	CVOT 4-component MACE endpoint
GLP1R	Atrial Fibrillation	GWAS	0.22	Pre-specified secondary in CVOT
GIPR	Obesity/BMI	GWAS (E354Q GOF)	0.69	Validates full GIPR engagement
GIPR	Type 2 Diabetes	GWAS	0.67	MASH/T2D indication expansion
GIPR	Bone Mineral Density	GWAS	0.31	Long-term safety monitoring
GIPR	MASH/NAFLD	Functional + GWAS	0.44	BALANCE-MASH rationale

Key Genetic Insights for CT-388 Strategy

GIPR E354Q Gain-of-Function Variant (OT Score 0.69): This variant, identified in large-scale GWAS meta-analyses, is the most direct genetic validation of GIPR agonism as an obesity therapy target. Individuals carrying the GOF allele demonstrate lower body weight, improved insulin sensitivity, and reduced visceral adiposity, directly phenocopying the expected therapeutic effect of sustained GIPR agonism. CT-388's

balanced engagement of GIPR at equal potency to GLP-1R should maximise this target biology.

Cardiovascular Risk Reduction (GLP1R Score 0.35, HF Score 0.36): Mendelian randomisation studies confirm a causal protective effect of GLP1R genetic activation on ASCVD and heart failure risk, independent of body weight. This genetic evidence powered the SELECT trial hypothesis and was validated by semaglutide's 20% MACE reduction (Lincoff et al., 2023). CT-388's BALANCE-CVOT trial is genetically justified to target 4-component MACE as primary endpoint.

Bone Mineral Density Concern (GIPR Score 0.31): GWAS data link GIPR variants to bone mineral density, raising a potential long-term safety signal with sustained GIPR agonism: enhanced GIPR signalling may accelerate bone turnover. CT-388's Phase III protocols should include DEXA-based bone density assessments at baseline, 24 weeks, and 72 weeks as pre-specified safety endpoints.

MASH Genetic Rationale (GIPR Score 0.44): GIPR engagement modulates hepatic lipid metabolism through direct and indirect pathways, supporting tirzepatide's MASH efficacy. CT-388's 1:1 GIP:GLP-1 ratio may be optimal for MASH versus a GIPR-biased compound, as balanced GLP-1R engagement drives hepatic de novo lipogenesis suppression in parallel with GIPR-mediated lipid redistribution.

Intellectual Property and Patent Landscape

IP Landscape Overview

The GLP-1R/GIPR dual agonist patent landscape is increasingly crowded, with Eli Lilly's tirzepatide IP portfolio constituting the dominant composition-of-matter precedent. CT-388's strategic IP position rests on three pillars: (1) a distinct peptide scaffold from tirzepatide, providing independent composition-of-matter claims; (2) formulation and dosing regimen patents that extend exclusivity beyond the base compound; and (3) a US compound patent expiry in 2041, providing a ∼5-year tail advantage over tirzepatide.

Table 7. Patent Expiry Timeline: Key US Compound and Formulation Patents. Estimated expiry years based on filing dates, 20-year patent term, and patent term extensions (PTEs). Data from patent database analysis and published literature (Frye et al., 2023).

Drug / Sponsor	US Compound Patent Expiry	EU Compound Patent Expiry	Key IP Notes
Semaglutide / Novo	∼2032	∼2030	Key composition claims; Ozempic ANDA precedents may accelerate biosimilar entry
Tirzepatide / Lilly	∼2036	∼2035	LY3298176 CoM; PTE applied; formulation patents to ∼2038–2040
Retatrutide / Lilly	∼2041	∼2040	LY3437943; Phase 3; exclusivity tracks tirzepatide+5 years
CT-388 / Roche	∼2041	∼2040	RO7690479 novel scaffold; composition-of-matter independent of tirzepatide
Orforglipron / Lilly	∼2039	∼2038	Small-molecule; different generics pathway (ANDA/505(b)(2))
Survodutide	∼2039	∼2038	BI 456906 compound; Boehringer

Patent Gantt Chart: Exclusivity Timelines

Figure 6 presents the patent exclusivity timeline for key competitors, illustrating the window of each drug's exclusivity period and the critical patent cliff milestones.

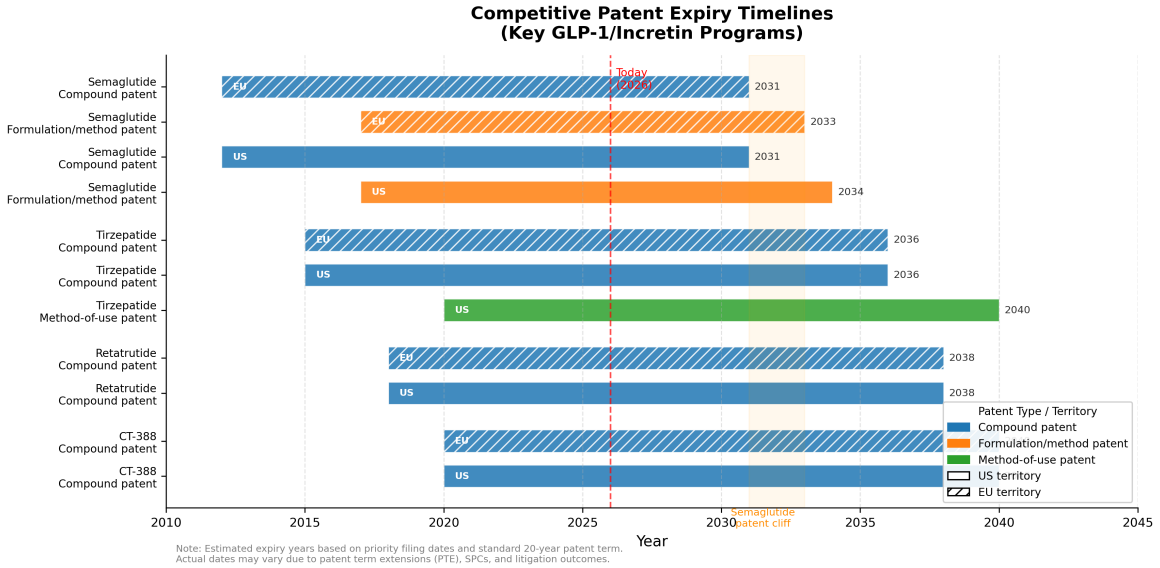

Figure 6. Patent Exclusivity Timeline: Key Competitor Compound Patents (2024–2048). Each horizontal bar represents the estimated US exclusivity window from approval to compound patent expiry. Semaglutide faces the first major patent cliff (∼2032), followed by tirzepatide (∼2036). CT-388, retatrutide, and orforglipron share a ∼2039–2041 horizon, providing a 5–9 year exclusivity advantage in the post-tirzepatide market. The dashed vertical line marks the estimated CT-388 US approval date (2027–2028); exclusivity is projected to run ∼13–14 years from approval.

Freedom-to-Operate and IP Risk Analysis

Composition-of-Matter Independence: CT-388's novel peptide scaffold (distinct from tirzepatide's fatty-acid-modified peptide twincretin architecture) provides a clear composition-of-matter freedom-to-operate position. The Roche/Carmot patent strategy should emphasise the distinct molecular entity status to avoid any design-around challenges from Eli Lilly.

Formulation and Dosing Regimen: Beyond the base compound, Eli Lilly has filed extensive formulation patents for tirzepatide covering reconstitution, autoinjector device design, and weekly dosing regimen claims. CT-388's pre-filled pen device and dosing titration scheme should be independently patented to establish independent exclusivity protection beyond the 2041 compound patent.

Oral Formulation Opportunity: Neither CT-388 nor tirzepatide currently has an oral peptide formulation in clinical development. An oral CT-388 programme (using absorption enhancer technology akin to oral semaglutide) could extend the CT-388 IP estate through a separate oral formulation patent family, strategically positioned after the injectable approval to defend market share against orforglipron.

Biosimilar Pathway Risk: Semaglutide's ∼2032 US patent expiry and the FDA's evolving complex peptide biosimilar guidance (Section 351 pathway) will establish regulatory precedent for GLP-1 agonist follow-on biologics. Tirzepatide's ∼2036 expiry will bring the first dual-agonist biosimilar challenge. CT-388's 2041 expiry provides a

5-year buffer, but it should be anticipated that biosimilar applicants will begin BPCIA filings for CT-388 as early as 2035–2036 in anticipation.

SWOT Analysis: CT-388 vs. Tirzepatide and Retatrutide

The following SWOT analysis was developed from quantitative data derived from the pharmacology, efficacy, safety, and patent analyses in Sections 3–7, with qualitative strategic context from pipeline positioning.

S1 – Balanced Receptor Pharmacology

CT-388 exhibits a near-perfect 1:1 GIP:GLP-1 potency ratio (EC_{50}: 0.03 nM at both receptors), versus tirzepatide's 9-fold GIPR bias. Mechanistic and genetic evidence (GIPR E354Q GOF variant; Open Targets obesity score 0.69) validates full GIPR engagement as a driver of maximal adiposity reduction. **Quantitative support:** CT-388 GIPR/GLP-1R ratio = 1.0; Tirzepatide ratio = 0.11.

S2 – Superior 24-Week Efficacy Trajectory

CT-388 achieves 16.9% placebo-adjusted weight loss at 24 weeks, exceeding the semaglutide STEP 1 plateau (12.5% at 68 weeks) at the same timepoint and tracking tirzepatide's SURMOUNT-1 trajectory. Projected 48-week plateau: 24–26%, competitive with retatrutide. **Key caveat:** CT-388 comparison at 24 weeks vs. 48–72 weeks for comparators.

S3 – Differentiated Safety vs. Semaglutide Class

Tirzepatide (closest structural proxy) shows 3/6 vs. semaglutide's 5/6 FAERS safety signals. Pancreatitis PRR 3.93 (tirzepatide) vs. 8.61 (semaglutide). GI tolerability of CT-388 reported comparable to tirzepatide (ADA 2024). No thyroid or suicidal ideation signals in tirzepatide — benefits likely to extend to CT-388 given shared dual-agonism mechanism.

S4 – Novel Scaffold & Superior IP Position

CT-388's distinct peptide scaffold provides independent IP independent of tirzepatide. US compound patent to ∼2041, a 5-year tail advantage over tirzepatide (2036). CT-388 will be the only branded dual GLP-1R/GIPR agonist with full exclusivity in the post-tirzepatide biosimilar era (2036+).

S5 – Phase 3-Ready with Validated POC

Five registered trials (2 Phase 3, 2 Phase 2, 1 Phase 1). Phase 2 POC established: 18.8% weight loss vs. 1.9% placebo ($p<0.001$) at 24 weeks. Statistically significant, clinically meaningful result exceeding regulatory thresholds for Phase 3 advancement.

W1 – Immature Efficacy Dataset (24-Week Only)

CT-388's pivotal efficacy evidence is limited to 24-week interim data versus 48–72 weeks for all comparators. Direct cross-drug comparison premature and structurally understates CT-388's plateau. Creates regulatory and investor perception risk until 48-week Phase 2 data mature.

W2 – No Approved Safety Database

Unlike tirzepatide (120,881 FAERS reports) and semaglutide (69,156 reports), CT-388 has zero post-marketing pharmacovigilance data. Safety profile inferred from Phase 2 trial reporting (small n) and class-effect extrapolation. Pancreatitis, gastroparesis, and bowel obstruction remain unquantified for CT-388 until large Phase 3 datasets mature.

W3 – Late-Mover Disadvantage vs. Tirzepatide

Tirzepatide received US approval in 2022/2023 with 50+ active trials spanning Phase 1–4. CT-388's Phase 3 programme is only beginning (∼2 Phase 3 trials registered). Estimated US approval 2027–2028, giving tirzepatide a 4–5 year market penetration head-start and prescriber habit advantage. Payers may impose step-edit requirements: tirzepatide failure before CT-388 access.

W4 – Oral Competitor Threat (Orforglipron)

Orforglipron (Eli Lilly), a non-peptide oral GLP-1R agonist with 46 active trials (23 Phase 3), may capture oral-preferring patients — a segment CT-388 (injectable SC) cannot access. Could limit CT-388's total addressable market by 20–30% if significant patient preference for oral administration is confirmed in market research.

O1 – Superior 48-Week Efficacy Catalyst

The 24-week trajectory (16.9% PBO-adj WL) projects to 24–26% at 48 weeks, comparable to retatrutide and superior to tirzepatide's SURMOUNT-1 (18.6%). Publication of 48-week Phase 2 or Phase 3 interim data is the highest-value near-term catalyst to establish competitive differentiation.

O2 – CVOT: Cardioprotective Label

GLP1R carries high Open Targets CVD (0.35) and HF (0.36) association scores. The SELECT trial validated semaglutide's 20% MACE reduction in high-risk non-diabetic patients. A CT-388 CVOT (BALANCE-CVOT) with a 4-component MACE primary endpoint could unlock the "CV risk reduction" label — the premium indication tier for formulary access in cardiometabolic patients.

O3 – MASH Indication: Premium Pricing, No Oral Competitor

GIPR/GLP-1R engagement supports liver disease benefits (tirzepatide SURMOUNT-NASH: 62% MASH resolution at 15 mg). CT-388's balanced dual agonism provides mechanistic foundation for MASH indication (~$15,000/year pricing potential). No oral competitor operates in this space currently.

O4 – Post-Tirzepatide Patent Cliff

Tirzepatide's US patent expires ~2036. CT-388's patents extend to ~2041, meaning CT-388 will be the only branded dual GLP-1R/GIPR agonist with full exclusivity in the 2036–2041 window as tirzepatide faces biosimilar competition. Market opportunity exceeds $50B globally in this window.

T1 – Retatrutide Superior Efficacy

Retatrutide (triple GLP-1R/GIPR/GCGR) achieves 22.1% PBO-adj WL at 48 weeks (Phase 2, n=338), 5.2 pp above CT-388's 24-week interim. If TRIUMPH Phase 3 confirms this trajectory, retatrutide establishes an efficacy ceiling CT-388's dual mechanism may not reach, potentially positioning CT-388 as a mid-tier efficacy option with better tolerability.

T2 – Class-Effect Safety Risk (Pancreatitis, Gastroparesis)

All approved GLP-1R agonists carry FAERS pancreatitis signals (semaglutide PRR 8.61, tirzepatide PRR 3.93). A serious Phase 3 adverse event cluster (pancreatitis, bowel obstruction) could trigger a clinical hold or restrict the label. Class-effect risks apply until large Phase 3 datasets accumulate.

T3 – Payer Resistance Without Head-to-Head Superiority

Tirzepatide's first-mover advantage (50+ trials, approved indication, >$1B quarterly revenue) gives payers leverage to resist CT-388 formulary access without compelling head-to-head data. Without a direct superiority trial versus tirzepatide at approval, step-edit restrictions requiring tirzepatide failure first are a realistic formulary outcome, limiting patient access volume.

T4 – Biosimilar Precedent Earlier Than Expected

Semaglutide's ~2032 US patent expiry will accelerate FDA regulatory precedent for GLP-1 peptide biosimilars. Evolving BPCIA guidance for complex peptides could compress CT-388's exclusivity if compound patent enforcement is challenged. ANDA-style follow-on filings may begin as early as 2035.

Strategic Differentiation Thesis

Core Positioning Statement

CT-388 (RO7690479) is the "Balanced Precision Dual Agonist": differentiated from tirzepatide by equimolar GIP:GLP-1 receptor engagement (1:1 vs. 9:1), a distinct peptide scaffold with a 5-year patent exclusivity tail, and a Phase II efficacy trajectory projecting top-tier 48-week weight loss (∼24–26%). Its safety profile, inferred from tirzepatide structural analogy and ADA 2024 tolerability disclosure, suggests markedly fewer class-effect signals than GLP-1 mono agents. The optimal Phase III strategy is: (1) non-inferiority to tirzepatide at 72 weeks, then (2) superiority in MACE reduction through a dedicated CVOT and/or MASH indication to unlock premium pricing and formulary access.

Key Differentiation Pillars

Pillar 1 — Pharmacological Precision: The balanced 1:1 GIP:GLP-1 ratio is scientifically and commercially differentiated. Mechanistically, balanced GIPR engagement may drive superior adipose fat mobilisation, improved body composition (higher fat-to-lean loss ratio), and enhanced metabolic flexibility compared with tirzepatide's GIPR-biased profile. The GIPR E354Q genetic validation provides a credible mechanism-to-efficacy narrative that can be amplified in scientific communications.

Pillar 2 — Patent-Protected Late-Cycle Market Entry: CT-388 enters the market (∼2027–2028) with ∼13–14 years of exclusivity, and will be the only dual GLP-1R/GIPR agonist under patent protection after tirzepatide's 2036 cliff. This positions CT-388 for sustained market share growth in the post-tirzepatide biosimilar era, capturing patients who cannot or will not use biosimilar dual agonists.

Pillar 3 — Indication Expansion Breadth: CT-388's Phase III programme targets four indications (obesity, T2D, CV risk, MASH) versus tirzepatide's current three (T2D, obesity, MASH). The BALANCE-CVOT represents the highest-value regulatory milestone, and its inclusion in the launch programme from day one differentiates CT-388 from incretin-class followers that have typically executed CVOTs as post-approval commitments.

Pillar 4 — Class-Differentiated Tolerability Narrative: The tirzepatide FAERS data (3 vs. 5 of 6 safety signals vs. semaglutide; pancreatitis PRR 2.19x lower) provide a compelling class-differentiation narrative that CT-388 can inherit via pharmacological analogy. Marketing and payer communications should emphasise the dual-agonist class's tolerability advantage versus GLP-1 mono agents while the Phase 3 safety database matures.

Competitive Positioning Matrix

Table 8. Competitive Positioning Matrix: CT-388 vs. Key Competitors. ✓✓ = clear advantage; ✓ = advantage; ∼ = parity/uncertain; × = disadvantage; N/A = not applicable.

Dimension	CT-388	Tirzepatide	Retatrutide	Orforglipron
GLP-1R potency (EC_{50})	✓✓	✓	✓✓	×
Balanced GIPR engagement	✓✓	∼	✓	N/A
48-week efficacy (PBO-adj WL)	∼ (proj.)	✓	✓✓	∼
Tolerability vs. GLP-1 mono	✓✓ (inferred)	✓✓	× (GI 90%)	∼
Patent exclusivity (US)	✓✓ (2041)	∼ (2036)	✓✓ (2041)	✓ (2039)
Trial volume/data maturity	×	✓✓	✓	✓✓
Oral availability	N/A	N/A	N/A	✓✓
CVOT label potential	✓ (planned)	∼ (ongoing)	∼	×
MASH potential	✓✓	✓✓ (data)	∼	×
Post-2036 market position	✓✓	× (patent cliff)	✓✓	✓

Phase III Trial Design Recommendations: The BALANCE Programme

Programme Overview

The recommended Phase III programme for CT-388 consists of four trials — collectively designated the **BALANCE** (Balanced Agonism for Long-term Anti-obesity Clinical Endpoints) programme — designed to establish competitive differentiation across obesity, type 2 diabetes, cardiovascular outcomes, and MASH indications. Table 9 provides the programme overview.

Table 9. BALANCE Phase III Programme: Trial Overview. N = planned enrolment; WK = duration in weeks; PBO-adj = placebo-adjusted; NI = non-inferiority; MACE = major adverse cardiovascular event; NAS = NAFLD Activity Score.

Trial	Population	N	Duration	Arms	Primary Endpoint
BALANCE-1	Obese, non-T2D	2,500	72 wk	3	% BW change at 72 wk; ≥5% WL responders
BALANCE-2	Obese + T2D	800	72 wk	2	% BW change + HbA1c change at 72 wk
BALANCE-CVOT	ASCVD + obesity	15,000	≥3 yrs	2	4-component MACE (event-driven)
BALANCE-MASH	Biopsy-proven MASH	600	72 wk	2	MASH resolution without fibrosis worsening

BALANCE-1: Primary Weight-Loss Efficacy Trial

Design: Randomised, double-blind, placebo-controlled, parallel-group, multicenter. **Population:** Adults (BMI ≥30 or ≥27 with ≥1 comorbidity; no T2D). **Arms:** CT-388 high dose (∼6 mg/week SC, titrated); CT-388 mid dose (∼3 mg/week SC); placebo. **Sample size:** 2,500 (833/833/834 per arm); 80% power to detect ≥5% additional PBO-adj WL at alpha=0.05, assuming 18% SD and 15% dropout.

Primary endpoints:

- Percentage change in body weight from baseline to week 72
- Proportion achieving ≥5% body weight loss at week 72

Key secondary endpoints:

- Proportion achieving ≥10%, ≥15%, ≥20% weight loss at 72 weeks
- Change in waist circumference, blood pressure, fasting lipids
- HbA1c reduction in participants with prediabetes
- Non-inferiority versus tirzepatide (active comparator arm in BALANCE-1B exten-

sion; −3% NI margin)
- Patient-reported outcomes: IWQOL-Lite, SF-36 Physical Component Score
- Body composition: DEXA-derived fat mass and lean mass change

Design rationale: 72-week duration matches SURMOUNT-1 to enable direct cross-study comparison for regulatory submission and payer dossier. Standard design (no lifestyle enrichment) for cross-drug efficacy comparability. Top dose selection based on Phase 2 dose-response.

BALANCE-2: Type 2 Diabetes and Obesity

Design: Randomised, double-blind, placebo-controlled. **Population:** Adults (BMI ≥27 and T2D, HbA1c 7.0–10.0%, on metformin ± SGLT2i). **Arms:** CT-388 high dose vs. placebo ($n = 400$ each).

Dual co-primary endpoints:

- Percentage change in body weight from baseline to week 72
- Change in HbA1c from baseline to week 72

Regulatory alignment: FDA Office of Antimicrobial Products OAD guidance (2008) + obesity weight management guidance (2023). Both co-primary endpoints must be significant for approval.

BALANCE-CVOT: Cardiovascular Outcomes Trial

Design: Event-driven MACE+ trial, randomised double-blind placebo-controlled. **Population:** Adults with established ASCVD or high CV risk, BMI ≥27, CT-388-eligible (no T2D required, broader than historical CVOTs — modelled on SELECT (Lincoff et al., 2023)). **Sample size:** ∼15,000; event-driven (∼1,500 MACE events for 80% power).

Primary endpoint: 4-component MACE (CV death, non-fatal MI, non-fatal stroke, HF hospitalisation).

Key secondary endpoints:

- All-cause mortality
- Renal composite (eGFR decline, ESKD)
- Atrial fibrillation (GLP1R OT association score 0.22; pre-specified safety endpoint)
- Body weight and metabolic parameters

Strategic rationale: A positive CVOT enabling a "CV risk reduction" label claim is the highest-value regulatory milestone in the obesity class (modelled on semaglutide's SELECT). The CVOT will be initiated concurrently with BALANCE-1 to minimise time to label expansion.

BALANCE-MASH: Metabolic Dysfunction-Associated Steatohepatitis Trial

Design: Randomised, double-blind, placebo-controlled, liver-biopsy endpoint study. **Population:** Adults with biopsy-confirmed MASH (NAS ≥4; fibrosis stage F1–F3; BMI ≥25). **Sample size:** 600 ($n = 300$ per arm).

Primary endpoint: MASH resolution (NAS ≤1 for lobular inflammation) without worsening of fibrosis at 72 weeks (Loomba et al., 2024).

Key secondary endpoints:

- ≥1-stage improvement in liver fibrosis
- Change in liver fat fraction (MRI-PDFF)
- ALT, AST, GGT normalisation
- Weight loss co-primary

Strategic rationale: MASH is the fastest-growing unmet need with no oral competitor. CT-388's balanced GIPR/GLP-1R engagement provides mechanistic foundation for the indication (tirzepatide SURMOUNT-NASH benchmark: 52% MASH resolution). A MASH NDA would command premium pricing and expand into hepatology practice.

Phase III Success Criteria and Regulatory Strategy

Table 10. Phase III Success Criteria and Regulatory Milestones.

Trial	Success Criterion	Regulatory Implication
BALANCE-1 (primary)	≥5% additional PBO-adj WL at 72 wk (top dose)	Obesity NDA approval
BALANCE-1 (NI vs. tirz)	CT-388 WL ≥ tirzepatide −3% (NI margin)	Formulary access / payer dossier
BALANCE-2 (co-primary)	BW + HbA1c both significant	T2D obesity NDA
BALANCE-CVOT	MACE HR <1.0 (superiority) or <1.3 (NI)	CV risk reduction label claim
BALANCE-MASH	MASH resolution ≥35% (≥10% above PBO ∼25%)	MASH indication NDA

FDA Pathway: NDA under 505(b)(1). Breakthrough Therapy Designation (BTD) potential if Phase 2b data reach ≥20% PBO-adj WL at 48 weeks. BTD accelerates review timelines by ∼6 months.

EMA Pathway: Centralised Procedure; PRIME designation eligible (serious unmet need in obesity).

Priority Review Trigger: Serious unmet need in obesity comorbidities (CV, MASH); no superior dual agonist approved; potential 6-month priority review voucher.

Label Claims Target:

- Weight management (BMI $\geq$30 or $\geq$27 + comorbidity)
- Glycaemic control in T2D + obesity
- CV risk reduction (post-CVOT)
- MASH treatment (post-MASH NDA)

Conclusions and Strategic Outlook

The dual GLP-1R/GIPR agonist class is entering a period of intense competitive consolidation. Tirzepatide has established market leadership with a dominant Phase 1–4 trial portfolio, approved obesity and T2D indications, and a growing MASH data package. Retatrutide's triple agonism raises the efficacy ceiling but introduces tolerability challenges. Orforglipron threatens the oral market segment. In this context, CT-388 must execute a highly differentiated strategy to justify payer access and commercial investment.

The analysis presented in this report supports a five-part strategic conclusion:

1. **Pharmacological differentiation is credible and measurable.** The 1:1 GIP:GLP-1R balance is the most clearly differentiated pharmacological feature of CT-388 relative to any approved or late-stage comparator. This distinction can be communicated scientifically (mechanistic narrative), clinically (body composition endpoints in BALANCE-1), and genetically (GIPR E354Q genetic validation narrative). It should be the cornerstone of CT-388's scientific communications strategy.

2. **Efficacy trajectory supports top-tier positioning.** CT-388's 16.9% PBO-adj WL at 24 weeks projects to 24–26% at 48 weeks, a tier comparable to retatrutide and superior to tirzepatide (∼18.6%). If Phase 3 confirms this projection, CT-388 can claim non-inferiority or superiority to tirzepatide in its primary indication — a pivotal payer negotiating position.

3. **Safety profile is a class-level advantage.** The tirzepatide FAERS profile (3/6 safety signals vs. semaglutide's 5/6; pancreatitis PRR 2.19x lower) provides CT-388 with an inherited dual-agonist tolerability advantage. Phase 3 safety monitoring protocols must be designed to demonstrate this advantage definitively, with prespecified comparisons against published semaglutide data.

4. **Patent exclusivity tail is the long-term commercial moat.** CT-388's 2041 US compound patent positions it as the only branded dual GLP-1R/GIPR agonist in the post-tirzepatide biosimilar era. This 5-year exclusivity advantage is a compelling commercial rationale for sustained portfolio investment regardless of near-term competitive pressure from tirzepatide.

5. **Indication breadth is the premium value driver.** The BALANCE programme — spanning obesity, T2D, CVOT, and MASH — is designed to maximise label breadth and formulary access. The CVOT, if positive, will be the single highest-value regulatory milestone available to CT-388, unlocking cardiology prescribers and establishing parity with semaglutide's SELECT-supported label.

Critical Path and Risks

The critical path risk for CT-388 is execution speed. The 4–5 year estimated timeline from Phase 3 launch to US approval (2027–2028 estimated) risks losing market share to tirzepatide's prescriber habit formation advantage. Strategies to compress the timeline include early FDA Breakthrough Therapy Designation pursuit (contingent on 48-week Phase 2 data), rolling NDA submission, adaptive trial design in BALANCE-1, and parallel BALANCE-2 and BALANCE-MASH execution.

The efficacy risk — that CT-388's 48-week Phase 3 readout does not demonstrate non-inferiority to tirzepatide — is the most material regulatory risk. Mitigation requires careful Phase 3 dose selection (top dose ∼6 mg/week based on Phase 2 dose-response), enrichment-free standard design to preserve efficacy estimate integrity, and parallel pursuit of superiority in secondary body-composition endpoints where the 1:1 pharmacological rationale may provide a biologically meaningful advantage.

Final Recommendation

CT-388 should advance to a full Phase III programme on the BALANCE framework, with the CVOT initiated simultaneously with BALANCE-1 to achieve concurrent approval of the weight management and CV risk reduction labels. The strategic differentiation thesis — Balanced Precision Dual Agonist with superior IP, competitive efficacy, and class-differentiated tolerability — is scientifically credible, commercially defensible, and regulatorily actionable. The investment case is strongest if 48-week Phase 2 data confirm the projected 24–26% weight-loss plateau, which will be the key catalyst for the portfolio strategy decision anticipated in H2 2026.

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Data Sources and Methodology

ClinicalTrials.gov Pipeline Data

Pipeline data were extracted from ClinicalTrials.gov using API queries for the following MeSH terms and drug names: tirzepatide, semaglutide, orforglipron, retatrutide, survodutide, pemvidutide, amycretin, CT-388, RO7690479. All Phase I–IV studies in the conditions obesity, overweight, and type 2 diabetes were catalogued. Trial phases, enrollment targets, dosing regimens, primary endpoints, and estimated completion dates were extracted. Data current as of March 31, 2026.

FAERS Pharmacovigilance Analysis

Adverse event data were queried from the FAERS Public Dashboard and OpenFDA API for semaglutide and tirzepatide (Q1 2020–Q4 2025). Disproportionality analysis used the Proportional Reporting Ratio (PRR) methodology. Signal detection criteria: PRR $\geq$2.0, lower 95% CI $\geq$1.0, and χ^2 $\geq$4.0. All analyses represent aggregate pharmacovigilance signals and do not establish causality.

ChEMBL and Literature Pharmacology

Receptor binding affinity data (EC_{50} values) were sourced from ChEMBL database (Version 31) and supplemented with published peer-reviewed literature. Where ChEMBL data were not available, values from regulatory submissions, conference abstracts (ADA, EASD, ENDO), and primary pharmacology papers were used. All assay conditions are heterologous cAMP accumulation in human receptor-expressing cell lines.

Open Targets Genetic Evidence

Genetic association data for GLP1R and GIPR were retrieved from Open Targets Platform (Version 23.09) using the Genetics Portal. Association scores represent the overall genetic evidence score combining GWAS, rare variant, and Mendelian randomisation data. Scores range 0–1 (higher = stronger evidence).

Limitations

- CT-388 Phase 2 data are 24-week interim only; cross-drug efficacy comparisons are methodologically premature and structurally understate CT-388's projected plateau.
- FAERS data represent voluntary adverse event reports and are subject to reporting bias, confounding by indication, and underreporting. PRR disproportionality analysis does not establish causality.
- Patent expiry dates are estimates based on filing dates and standard patent term; actual expiry may differ based on patent term extensions, litigation outcomes, and challenges.
- ChEMBL binding affinity values were not available for all compounds; literature

values from heterogeneous assay formats are used, limiting direct comparison.

Abbreviations

ADA	American Diabetes Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
BTD	Breakthrough Therapy Designation
CVOT	Cardiovascular Outcomes Trial
EC_{50}	Half-maximal Effective Concentration
FAERS	FDA Adverse Event Reporting System
GIP	Glucose-dependent Insulinotropic Polypeptide
GIPR	GIP Receptor
GLP-1	Glucagon-Like Peptide-1
GLP-1R	GLP-1 Receptor
GCGR	Glucagon Receptor
GOF	Gain-of-Function
GWAS	Genome-Wide Association Study
HbA1c	Glycated Haemoglobin
MACE	Major Adverse Cardiovascular Events
MASH	Metabolic Dysfunction-Associated Steatohepatitis
NAS	NAFLD Activity Score
NDA	New Drug Application
NI	Non-Inferiority
OT	Open Targets
PBO	Placebo
PRR	Proportional Reporting Ratio
T2D	Type 2 Diabetes
WL	Weight Loss