M5.1 — Trial Portfolio Summary Cards

Trial Portfolio Summary Cards — Module 5

Use: Bedside / chart-side trial-evidence lookup for the 20 trials that anchor Module 5 clinical decision-making (GLP-1, GIP coagonist, triagonist, dual GLP-1/glucagon, amylin, and oral non-peptide classes; plus the foundational lifestyle, biology-of-defense, and class-safety trials).
Companion to: M5.1 v3 (Hormonal/Metabolic/Neural Drivers), M5.2 v3 (Semaglutide Deep Dive), M5.3 v3 (Tirzepatide), M5.4 v3 (Liraglutide / Triagonists / Combo-Products comparator landscape).
Print: Designed to fit one trial per scannable card so a clinician can answer "what did that trial actually show?" in <30 seconds at the point of care.

How to use this document

Each card distills a single trial down to the eight facts that matter most in a clinical conversation: trial name, NCT or PMID (clickable), publication year, sample size, design, population, primary endpoint, headline result, and a one-line applicability note. Cards are grouped by mechanism class and clinical purpose: (1) FDA-approved GLP-1 / GIP / amylin agents with mature Phase 3 evidence, (2) the pre-FDA-approval frontier (retatrutide, survodutide, orforglipron, CagriSema), (3) the indication-extension and discontinuation/maintenance trials, (4) the foundational lifestyle and set-point-biology anchors, and (5) the class-safety synthesis literature.

Effect sizes, sample sizes, and confidence intervals are drawn from M5.1–M5.4 v3 lesson bodies (which were verified against PubMed and ClinicalTrials.gov in the v3 production cycle). Any number that could not be confirmed in those sources is marked **"verify before use"** — do not cite that number in clinical documentation or patient counseling without a fresh primary-source check. For sponsor-disclosed Phase 3 toplines that have not yet appeared in peer-reviewed publication (TRIUMPH-4, SYNCHRONIZE-1), Pattern AA framing applies: cite as sponsor topline, not as published Phase 3 result.

Section 1 — FDA-Approved GLP-1 / GIP / Amylin Agents (Anchor Trials)

1. STEP 1 — semaglutide 2.4 mg in obesity without diabetes

Field	Detail
PMID	33567185 — Wilding JPH et al, *NEJM* 2021;384:989-1002
Year	2021
N	1,961
Design	Phase 3 double-blind placebo-controlled RCT, 68 weeks
Population	Adults BMI ≥30 (or ≥27 + weight-related comorbidity); without T2D
Primary endpoint	Percent change in body weight at 68 weeks
Headline result	Semaglutide **−14.9% body weight** vs placebo −2.4% at 68 weeks
Applicability	The load-bearing efficacy anchor for semaglutide 2.4 mg as first-line single GLP-1 RA in the appetite-driven obesity phenotype.

2. SELECT — semaglutide CV outcomes in obesity + established CVD without diabetes

Field	Detail
PMID	37952131 — Lincoff AM et al, *NEJM* 2023;389:2221-2232
Year	2023
N	17,604
Design	Phase 3 double-blind placebo-controlled cardiovascular outcomes RCT, median follow-up ~40 months

Field	Detail
Population	Adults BMI ≥27 + established CVD; without T2D
Primary endpoint	First MACE (composite: CV death, non-fatal MI, non-fatal stroke)
Headline result	Semaglutide **HR 0.80 (95% CI 0.72–0.90), P<0.001 — 20% relative MACE reduction**
Applicability	Basis for the March 8, 2024 Wegovy MACE-reduction indication; the trial to cite for the obesity-without-T2D patient with established CVD.

3. SURMOUNT-1 — tirzepatide in obesity without diabetes (registration trial)

Field	Detail
PMID	35658024 — Jastreboff AM et al, *NEJM* 2022;387:205-216
Year	2022
N	2,539 (1:1:1:1 to 5 mg / 10 mg / 15 mg / placebo)
Design	Phase 3 double-blind placebo-controlled RCT, 72 weeks
Population	Adults BMI ≥30 (or ≥27 + weight-related comorbidity); without T2D
Primary endpoint	Percent change in body weight at 72 weeks
Headline result	Tirzepatide 15 mg **–20.9% body weight (treatment-regimen estimand)** vs placebo at 72 weeks; efficacy estimand ~–22.5%
Applicability	The mechanism-ceiling anchor for dual GLP-1/GIP coagonism in unselected adult obesity; the trial that re-set the maximum single-agent magnitude expectation.

4. SURMOUNT-5 — tirzepatide vs semaglutide 2.4 mg head-to-head

Field	Detail
PMID	40353578 — Aronne LJ et al, *NEJM* 2025;393:26-36
Year	2025 (published July 3; epub May 11)
N	751
Design	Phase 3 open-label head-to-head RCT at max-tolerated doses, 72 weeks
Population	Adults with obesity without T2D
Primary endpoint	Percent change in body weight at 72 weeks
Headline result	Tirzepatide **−20.2%** vs semaglutide **−13.7%** — 6.5 pp absolute difference favoring tirzepatide; P<0.001
Applicability	The single most important head-to-head trial in current obesity pharmacotherapy — the load-bearing comparator anchor for any “which one first?” conversation.

5. SURMOUNT-OSA — tirzepatide for obstructive sleep apnea with obesity

Field	Detail
PMID	38912654 — Malhotra A et al, *NEJM* 2024;391:1193-1205
Year	2024 (published October 3)
N	Two-trial Phase 3 design supporting FDA approval (per-trial N: verify before use)
Design	Phase 3 dual-trial design: Trial 1 (CPAP-naïve) and Trial 2 (CPAP-current)
Population	Adults with moderate-to-severe OSA + obesity
Primary endpoint	Change in apnea-hypopnea index (AHI) at 52 weeks

Field	Detail
Headline result	Trial 2 (CPAP-current): AHI reduction **−29.3 events/hour on tirzepatide vs −5.5 on placebo**; mean weight reduction −20.1% on tirzepatide
Applicability	Basis for the December 20, 2024 FDA Zepbound OSA-with-obesity approval — the first FDA approval of any pharmacological agent for OSA with obesity.

6. ESSENCE — semaglutide for MASH F2/F3 fibrosis

Field	Detail
PMID	40305708 — Sanyal AJ, Newsome PN, Kliers I et al, *NEJM* 2025;392(21):2089-2099
Year	2025
N	800 (interim Part 1 analysis: n=534 semaglutide, n=266 placebo)
Design	Phase 3 double-blind placebo-controlled RCT, 72 weeks; histology-based dual primary endpoints
Population	Biopsy-proven MASH with F2 or F3 fibrosis (non-cirrhotic)
Primary endpoint	(1) MASH resolution without worsening fibrosis; (2) fibrosis improvement without worsening MASH
Headline result	MASH resolution **62.9% vs 34.3%** (+28.6 pp, P<0.001); fibrosis improvement **36.8% vs 22.4%** (+14.4 pp, P<0.001)
Applicability	Basis for the August 15, 2025 Wegovy MASH F2/F3 indication. Note the cirrhosis caveat — F4 Phase 2 (Loomba 2023, PMID 36934740) did NOT meet primary endpoint.

Section 2 — Discontinuation, Maintenance & Set-Point Defense

7. SURMOUNT-4 — tirzepatide withdrawal vs continuation (chronic-therapy anchor)

Field	Detail
PMID	38078870 — Aronne LJ et al, *JAMA* 2024;331(1):38-48
Year	2024
N	670 (randomized after lead-in)
Design	Phase 3 randomized-withdrawal: 36-week tirzepatide titration lead-in (mean −20.9%), then 52-week randomization to continue vs placebo
Population	Adults with obesity completing tirzepatide induction phase
Primary endpoint	Percent change in body weight at week 88 (from randomization to week 52)
Headline result	Tirzepatide continuation **additional −5.5%**; placebo switch **+14.0% regain**; 89.5% vs 16.6% maintained ≥80% of run-in loss
Applicability	The empirical anchor for chronic-therapy framing — "this is not a course to complete, it is chronic management of a chronic neuroendocrine disease."

8. STEP 1 Extension — semaglutide regain after discontinuation (Wilding 2022)

Field	Detail
PMID	35441470 — Wilding JPH, Batterham RL, Davies M et al, *Diabetes Obes Metab* 2022;24(8):1553-1564
Year	2022
N	327 (extension cohort from parent STEP 1)

Field	Detail
Design	One-year off-treatment follow-up after the 68-week STEP 1 RCT
Population	STEP 1 completers (semaglutide 2.4 mg or placebo arm) at week 68 → followed to week 120
Primary endpoint	Body weight trajectory 52 weeks after withdrawal of semaglutide + lifestyle intervention
Headline result	Patients regained **approximately two-thirds of lost weight on average** by 52 weeks off-treatment; cardiometabolic improvements largely reversed
Applicability	The companion anchor to SURMOUNT-4 — semaglutide and tirzepatide both show the same class-pattern regain trajectory after discontinuation.

9. Sumithran 2011 — hormonal adaptation persistence at 62 weeks post-loss

Field	Detail
PMID	22029981 — Sumithran P, Prendergast LA, Delbridge E et al, *NEJM* 2011;365:1597-1604
Year	2011
N	50 (34 completers at 62 weeks)
Design	Prospective cohort: 10-week very-low-energy diet, then 1-year follow-up with serial hormone and appetite measurement
Population	Adults with overweight or obesity (no diabetes) achieving ≥10% loss on VLED
Primary endpoint	Serial circulating concentrations of appetite-regulating hormones + subjective hunger/satiety
Headline result	Ghrelin, GIP, PYY, leptin, CCK, insulin, and amylin **all persistently altered in the appetite-stimulating direction at 62 weeks** post-loss; subjective hunger increased

Field	Detail
Applicability	The mechanistic anchor for why lifestyle-only weight loss fails — biology defends the prior set point with measurable, persistent hormonal shifts. Pair with Fothergill 2016 (Biggest Loser, PMID 27136388) for the energy-expenditure half.

Section 3 — The Pre-FDA-Approval Frontier

10. TRIUMPH-4 — retatrutide in obesity + knee osteoarthritis (sponsor topline)

Field	Detail
NCT	NCT05931367 — Eli Lilly LY3437943 (GLP-1/GIP/glucagon triagonist)
Year	Topline disclosed 2025-12-11; **peer-reviewed PMID pending**
N	445
Design	Phase 3 double-blind placebo-controlled RCT, 68 weeks; indication-specific (obesity + knee OA)
Population	Adults with obesity or overweight + knee osteoarthritis
Primary endpoint	Percent change in body weight at 68 weeks
Headline result	Retatrutide 12 mg **−28.7% body weight** vs placebo (sponsor topline; full per-protocol + sensitivity analyses pending publication — **verify before use** for any number beyond the headline magnitude)
Applicability	Establishes the triagonist-class effect-size ceiling above the dual-incretin and single-GLP-1 classes. Pattern AA: cite as sponsor topline, not as published Phase 3 result.

11. REDEFINE-1 — CagriSema (cagrilintide + semaglutide 2.4/2.4 mg) in obesity without T2D

Field	Detail
PMID	40544433 — Garvey WT et al, *NEJM* 2025
Year	2025
N	3,417
Design	Phase 3 four-arm RCT, 68 weeks: CagriSema vs cagrilintide-alone vs semaglutide-alone vs placebo
Population	Adults BMI ≥30 (or ≥27 + weight-related comorbidity); without T2D
Primary endpoint	Percent change in body weight at 68 weeks
Headline result	CagriSema **−22.7%**; semaglutide-alone −16.1%; cagrilintide-alone −11.8%; placebo −2.3 to −3.0% (approximately additive — not synergistic — combination effect)
Applicability	The first amylin + GLP-1 fixed-dose combination product to reach Phase 3; Novo Nordisk regulatory dossier submitted. Investor-context "fell short of 25% guidance" framing is share-price commentary, not a clinical characterization.

12. ATTAIN-1 — orforglipron (oral non-peptide GLP-1 RA) in obesity

Field	Detail
PMID	40960239 — Wharton S et al, *NEJM* 2025;393(19):1889-1901
Year	2025
N	3,127
Design	Phase 3 double-blind placebo-controlled RCT, 72 weeks; dose-finding (6 / 12 / 36 mg vs placebo)
Population	Adults with obesity (no T2D)

Field	Detail
Primary endpoint	Percent change in body weight at 72 weeks
Headline result	Orforglipron 36 mg **–11.2%** (95% CI –12.0 to –10.4); 12 mg –8.4%; 6 mg –7.5%; placebo –2.1%
Applicability	First oral non-peptide small-molecule GLP-1 RA to reach Phase 3 publication. Companion T2D trial: **ACHIEVE-1** (PMID 40544435, Rosenstock 2025) — HbA1c reductions –1.24% to –1.48% across dose arms vs placebo –0.41% over 40 weeks. FDA NDA submission anticipated end-2025 (obesity) / 2026 (T2D).

13. SYNCHRONIZE-1 — survodutide (GLP-1/glucagon dual) in obesity without T2D

Field	Detail
NCT	NCT06066515 — Boehringer Ingelheim / Zealand BI 456906
Year	Topline disclosed April 2026; **peer-reviewed PMID pending**
N	~4,734 (per ClinicalTrials.gov registration — **verify before use**)
Design	Phase 3 double-blind placebo-controlled RCT, 76 weeks
Population	Adults with obesity without T2D
Primary endpoint	Percent change in body weight at 76 weeks
Headline result	Survodutide 6.0 mg **~–16.6% body weight** vs placebo (Boehringer Ingelheim sponsor topline disclosure; full effect-size precision + safety reporting pending peer-reviewed publication)
Applicability	The mechanism-class-distinctive trial for direct hepatic GCGR engagement (relevant to MASH + obesity phenotypes); FDA Breakthrough Therapy designation for MASH. Pattern AA: cite as sponsor topline.

Section 4 — Foundational Lifestyle & Phenotyping Anchors

14. Look AHEAD — intensive lifestyle intervention in T2D + obesity

Field	Detail
PMID	23796131 — Wing RR et al (Look AHEAD Research Group), *NEJM* 2013;369:145-154
Year	2013
N	5,145
Design	RCT: intensive lifestyle intervention (ILI) vs diabetes-support-and-education control; median 9.6-year follow-up (max 13.5 years); stopped early for futility on CV endpoint
Population	Adults with T2D + overweight/obesity
Primary endpoint	Composite cardiovascular outcome (CV death, non-fatal MI, non-fatal stroke, hospitalization for angina)
Headline result	ILI weight loss **8.6% at year 1 → 6.0% at study end**; control 0.7% (yr 1) → 3.5% (end). **No reduction in MACE** — primary CV endpoint not met.
Applicability	The historical anchor for "lifestyle intervention works for weight, but not enough to prevent CV events in T2D + obesity." Frames why pharmacotherapy became the rate-limiting input.

15. Diabetes Prevention Program (DPP) — lifestyle vs metformin for diabetes prevention

Field	Detail
PMID	11832527 — Knowler WC et al (DPP Research Group), *NEJM* 2002;346:393-403
Year	2002

Field	Detail
N	3,234
Design	RCT: intensive lifestyle vs metformin 850 mg BID vs placebo; mean follow-up 2.8 years
Population	Adults with elevated fasting + post-load glucose (impaired glucose tolerance), BMI ≥24
Primary endpoint	Incidence of type 2 diabetes
Headline result	Lifestyle **reduced T2D incidence by 58% (95% CI 48–66%)**; metformin reduced by 31%. Mean lifestyle-arm weight loss ~5.6 kg (~6% body weight) vs ≥7% protocol target.
Applicability	The historical anchor for "weight loss is the dominant predictor of diabetes-incidence risk reduction" — Hamman 2006 follow-up (PMID 16936160) quantified each 1-kg loss reduced diabetes incidence by 16%.

16. Acosta 2021 — phenotype-guided antiobesity medication selection

Field	Detail
PMID	33759389 — Acosta A, Camilleri M, Abu Dayyeh B et al, *Obesity (Silver Spring)* 2021;29(4):662-671
Year	2021
N	Pragmatic trial cohort in obesity clinic (specific N: **verify before use**)
Design	Pragmatic non-randomized comparative cohort: phenotype-guided vs standard-care AOM selection across the four-phenotype framework ("hungry brain," "emotional hunger," "hungry gut," "slow burn")
Population	Adults attending an academic obesity clinic
Primary endpoint	Percent body weight change at 12 months
Headline result	**Phenotype-guided 15.9% mean weight loss vs 9.0% non-phenotype-guided at 12 months —**

Field	Detail
	1.75-fold difference
Applicability	The empirical anchor for the four-phenotype framework that Module 5 uses for first-line agent selection (M5.1 §3 — adapted to the current mechanism-class taxonomy).

Section 5 — Class-Safety Synthesis Evidence

17. Bjerre Knudsen 2010 — rodent C-cell signal (basis for MTC class-label boxed warning)

Field	Detail
PMID	20203154 — Bjerre Knudsen L, Madsen LW, Andersen S et al, *Endocrinology* 2010;151(4):1473-1486
Year	2010
N	Rodent mechanistic study (rats + mice; specific cohort sizes: **verify before use**)
Design	Preclinical (rodent) mechanism study + cross-species exposure-response comparison
Population	Rats, mice; comparison to non-human primate and human C-cell GLP-1R expression data
Primary endpoint	C-cell calcitonin release, calcitonin gene up-regulation, C-cell hyperplasia
Headline result	GLP-1 RA stimulated calcitonin release + C-cell hyperplasia in rats (and to a lesser extent mice). **Species-specific** — humans + primates have minimal thyroid C-cell GLP-1R expression and did not show comparable calcitonin responses at exposures >60× the human therapeutic dose.

Field	Detail
Applicability	The mechanistic basis for the MTC / MEN2 absolute contraindication on all GLP-1 RA labels. The contraindication is firm; the rodent-to-human extrapolation is the open question.

18. Ko 2026 — cancer risk SR + meta-analysis (GLP-1 RA and dual agonists)

Field	Detail
PMID	41359966 — Ko A, Chang YC, Bahar F et al, *Ann Intern Med* 2026 Feb (epub 2025-12-09)
Year	2026 (epub 2025-12)
N	48 RCTs, n=94,245
Design	Systematic review + meta-analysis of RCTs with GRADE certainty assessment
Population	Pooled RCTs of GLP-1 receptor agonists and dual agonists (across T2D, obesity, MASH, kidney, and CV outcomes trial populations)
Primary endpoint	Cancer incidence by anatomic site
Headline result	**Moderate-certainty evidence** that GLP-1 RAs and dual agonists **"probably have little or no effect on risk for thyroid cancer"** and similar minimal effects on pancreatic, breast, and kidney cancers; other obesity-related cancers uncertain / low certainty.
Applicability	The contemporary evidence-state anchor for patient counseling on cancer risk outside the MTC/MEN2 contraindication. Note authors' explicit caveat: trials were not designed to evaluate cancer outcomes; follow-up was short.

19. Wen 2025 — pancreatitis + pancreatic cancer SR + meta-analysis

Field	Detail
PMID	40988099 — Wen J, Nadora D, Bernstein E et al, *Endocrinol Diabetes Metab* 2025;8(5):e70113
Year	2025
N	62 RCTs, n=66,232
Design	Systematic review + meta-analysis of randomized controlled trials
Population	Pooled RCTs of GLP-1 receptor agonists across T2D and obesity indications
Primary endpoint	Acute pancreatitis incidence; pancreatic cancer incidence
Headline result	**Acute pancreatitis RR 1.44 (95% CI 1.09–1.89, P=0.009)** — modest but statistically significant relative-risk elevation. **Pancreatic cancer overall RR 1.30 (95% CI 0.86–1.97; non-significant);** subgroup with background medications RR 1.85 (95% CI 1.05–3.26).
Applicability	The class-level pancreatitis-signal anchor — small increased relative risk exists, absolute event rates remain low (<1–2%/year), discontinue if acute pancreatitis develops. Frame as Pattern V: signal present but modest, not alarm-level.

20. Bezin 2023 — French nationwide thyroid cancer case-control

Field	Detail
PMID	36356111 — Bezin J et al, *Diabetes Care* 2023
Year	2023
N	French National Health Data System cohort (specific case + control N: **verify before use**)
Design	Nested case-control within French nationwide cohort; 1–3 year GLP-1 RA exposure window

Field	Detail
Population	Adults in French national health database; T2D-treated cohort
Primary endpoint	All thyroid cancer; medullary thyroid cancer specifically
Headline result	**aHR 1.58 for all thyroid cancer; aHR 1.78 for medullary thyroid cancer** with 1–3 years of GLP-1 RA exposure
Applicability	The strongest published positive thyroid-cancer signal in the GLP-1 RA literature; **not consistently reproduced** in subsequent cohort studies, and contextualized by the Ko 2026 meta-analytic synthesis ("little or no effect," moderate certainty). One reason post-marketing surveillance continues.

Reviewer note

Cards drafted 2026-05-26 from M5.1 v3 + M5.2 v3 + M5.3 v3 + M5.4 v3 lesson bodies (verified against PubMed and ClinicalTrials.gov in the v3 production cycle). Sponsor-disclosed Phase 3 toplines (TRIUMPH-4, SYNCHRONIZE-1) cited under Pattern AA framing pending peer-reviewed publication. Numbers flagged **"verify before use"** are items where the lesson body source did not provide a specific figure at the granularity needed for the card — verify against PubMed or ClinicalTrials.gov before citing in chart notes, patient counseling, or any externally-facing material. Clinical-judgment items (which trial best fits a given patient, how to weigh moderate-certainty SR evidence against a positive nationwide cohort signal) route to Dr. Gross per the standing review framework.

Companion documents in this series: Doc 1 — Baseline Labs Checklist · Doc 5 — Hormone-Optimization Peptide Reference Card · Doc 10 — Five Safety Fronts Deep Dive · Doc 11 — M5.1 Knowledge Check (CME-style).