Favorable and unfavorable findings on Liraglutide

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Randomised trials and meta-analyses report that liraglutide produces moderate weight loss, glycaemic improvements, and cardiovascular risk reduction in adults with type 2 diabetes or obesity, yet these occur alongside frequent gastrointesti

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Randomised controlled trials, including the SCALE programme for weight management and the LEADER cardiovascular outcomes trial, together with numerous meta-analyses published through 2026, describe dose-dependent reductions in body weight, HbA1c, and major adverse cardiovascular events in selected populations. These favourable metabolic and cardiovascular signals are consistently placed next to high rates of gastrointestinal adverse events that drive discontinuation, increased biliary events, a precautionary safety signal for thyroid C-cell tumours based on rodent toxicology, and variable effects on lean body mass and quality of life. Evidence certainty ranges from moderate for weight-loss responder rates to very low for long-term sustainability and certain safety endpoints.



Abstract triptych separating reported favorable (left), null/mixed (center), and unfavorable (right) findings on liraglutide from indexed literature.

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Chemical Identity and Catalog Context

Liraglutide ($C_{172}H_{265}N_{43}O_{51}$, CAS 204656-20-2) features an Arg34 substitution and a palmitic acid side chain attached to Lys26 via a γ-glutamyl spacer, conferring albumin binding and extended half-life relative to native GLP-1. It is catalogued as a single, chemically defined research compound distinct from mixtures or tissue extracts. The present summary complements the earlier catalog entry focused on structural design, receptor pharmacology, preclinical models, and broad trial architectures by concentrating exclusively on the balance of reported favourable outcomes versus unfavourable tolerability and safety signals across indexed literature.

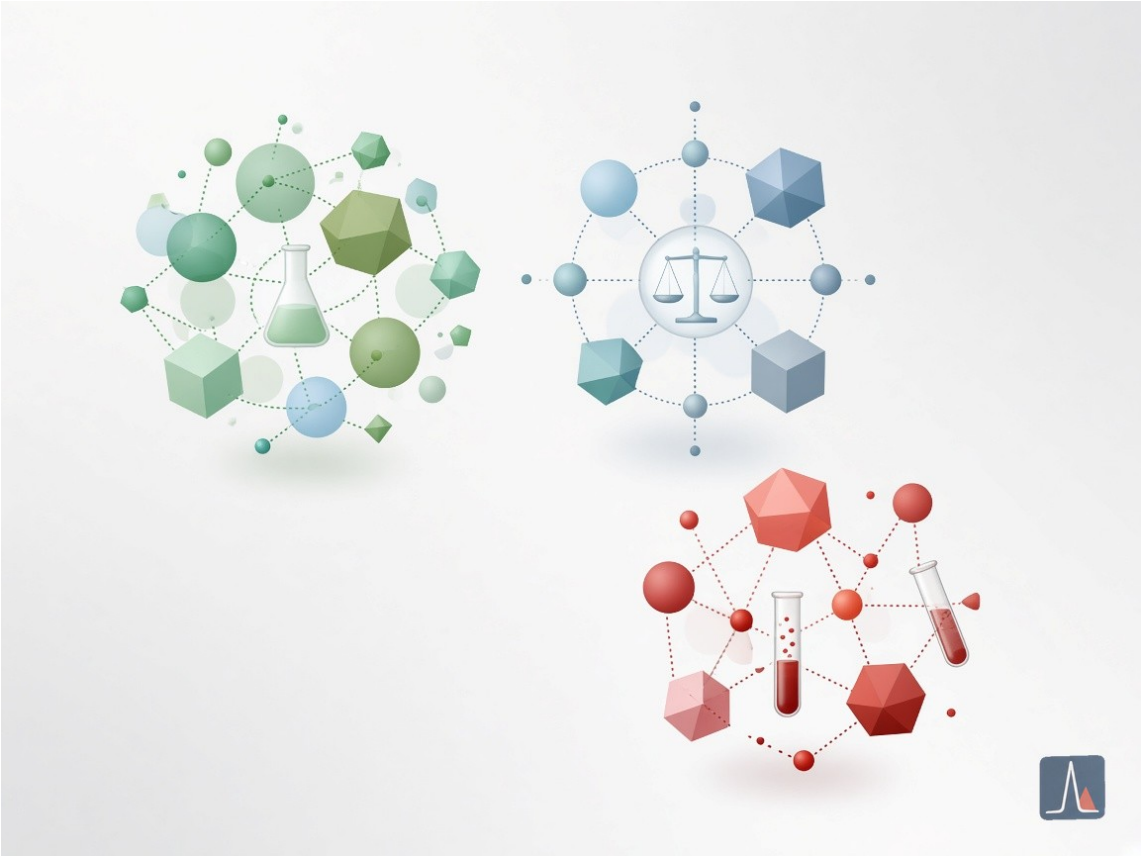
Favorable Clinical Findings from Randomised Trials and Meta-Analyses

The LEADER trial (Marso et al., 2016) randomised 9340 patients with type 2 diabetes and high cardiovascular risk to liraglutide (up to 1.8 mg daily) or placebo for a median 3.8 years. The primary composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke occurred in 13.0% versus 14.9% of participants (HR 0.87, 95% CI 0.78–0.97; P=0.01 for superiority). Cardiovascular death (4.7% vs 6.0%; HR 0.78) and all-cause mortality (8.2% vs 9.6%; HR 0.85) were also lower. Subsequent meta-analyses of randomised trials in type 2 diabetes (2024–2026) have corroborated reductions in major adverse cardiovascular events (RR approximately 0.85), myocardial infarction, and all-cause mortality, with some evidence of renal benefit via reduced progression of albuminuria. 1 2

In obesity or overweight populations, the SCALE programme and subsequent meta-analyses report placebo-corrected weight loss of approximately 4–6 kg or 4–8% at the 3.0 mg dose. A 2025 Cochrane review of liraglutide versus placebo in adults living with obesity found moderate-certainty evidence that liraglutide approximately doubles the proportion of participants achieving at least 5% weight loss (RR 2.10, 95% CI 1.80–2.45) at medium-term follow-up; this effect appeared sustained at longer-term assessment in available studies. Mean percentage weight change was approximately –4.7% (very low certainty). Glycaemic parameters improved in participants with type 2 diabetes (HbA1c reductions of 0.2–1.2% across doses in 2026 meta-analyses of 25 RCTs involving over 10 000 participants). Additional favourable signals include reductions in blood pressure, selected lipids (triglycerides), liver enzymes in non-alcoholic fatty liver disease cohorts, and delayed progression to type 2 diabetes in prediabetic individuals (approximately 79% relative risk reduction in one SCALE extension).

Meta-analyses of randomised trials have also reported improvements in BMI, waist circumference, and certain inflammatory or oxidative stress markers. In selected subgroups, exploratory benefits on executive function or post-bariatric weight maintenance have been described, although these are less consistently replicated.

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Abstract diagram illustrating the distribution of favorable, null, and unfavorable reported findings across randomised trials and meta-analyses of liraglutide.

Unfavorable Tolerability, Safety, and Body-Composition Findings

Gastrointestinal adverse events constitute the dominant tolerability limitation. Pooled data indicate nausea in 20–40% of participants (often peaking during dose escalation), vomiting, diarrhoea, and constipation, with overall gastrointestinal event rates approximately 68% versus 39% on placebo. These events are the leading cause of discontinuation; the 2025 Cochrane review reported increased risk of any adverse events (RR 1.07), serious adverse events (RR 1.20), and withdrawal due to adverse events (RR approximately 2.0). Discontinuation rates in weight-management trials frequently reached 7–14% versus lower rates with placebo or certain weekly comparators.

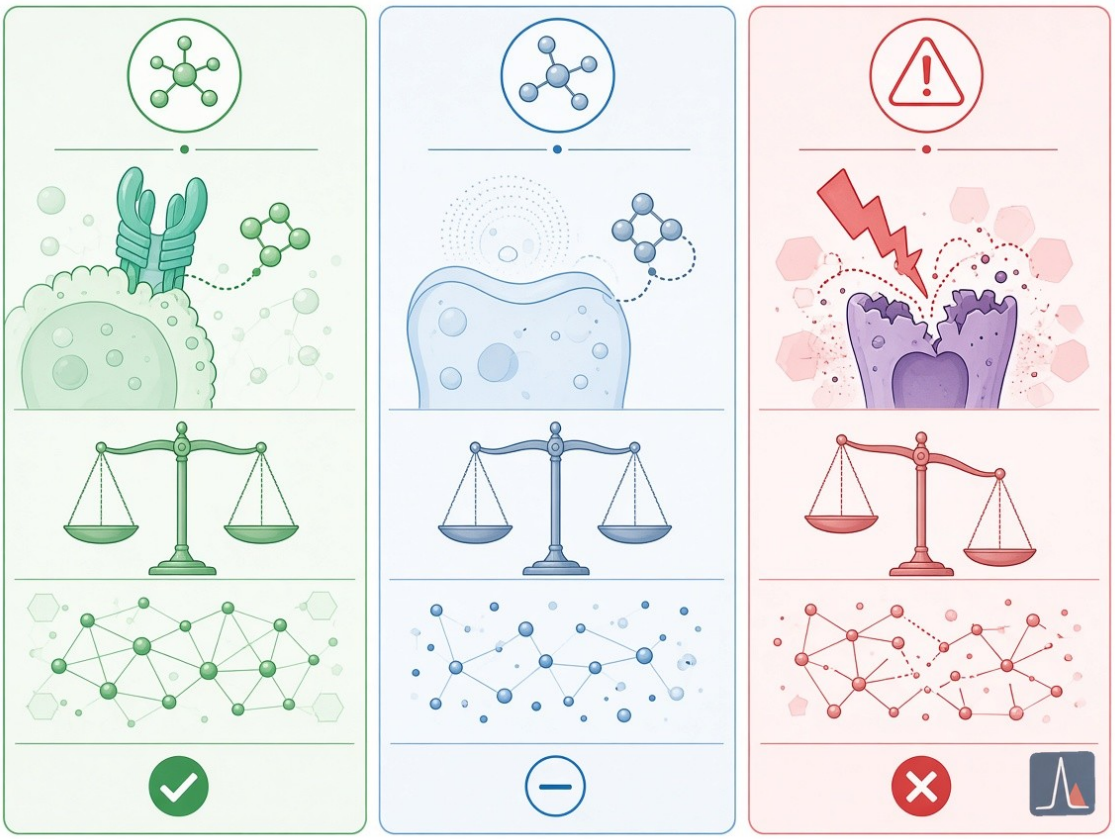
Gallbladder and biliary events are elevated (RR 1.3–2.3 in weight-loss populations), attributed to rapid weight reduction, altered motility, and bile stasis; cholelithiasis and cholecystitis rates were approximately 2.5% versus 1% in SCALE trials. Pancreatitis carries a product label warning; although LEADER showed numerically similar incidence (0.4% vs 0.5%), some class meta-analyses report modest risk elevations, and post-marketing reports include severe cases.

Preclinical rodent studies demonstrated dose-dependent C-cell hyperplasia, adenomas, and carcinomas at exposures relevant to human use, prompting a boxed warning for medullary thyroid carcinoma and contraindication in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2. Human data remain mixed: certain 2024–2025 meta-analyses of randomised trials reported a modest increase in overall thyroid cancer (OR approximately 1.5, fragile index low, NNH ~1350 over 5 years), while larger

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2026 pooled analyses of clinical trials, post-marketing surveillance, and real-world cohorts found no statistically significant elevation after accounting for detection bias. Absolute event rates remained low (<0.1%).

Body-composition data indicate that 25–40% of total weight lost may derive from lean mass, raising theoretical concerns for sarcopenia, particularly in older adults or those with low baseline muscle. Some meta-analyses also note increases in bone resorption markers and modest reductions in bone mineral density at certain sites, although fracture data are inconclusive. Heart rate increases of 2–9 bpm have been observed. When liraglutide is combined with insulin or sulfonylureas, hypoglycaemia risk rises.



Geometric panels separating favorable clinical signals, mixed or null outcomes, and unfavorable safety and tolerability data.

Null, Mixed, or Inconclusive Reported Findings

Comparative network meta-analyses consistently rank liraglutide below semaglutide 2.4 mg and tirzepatide for magnitude of weight loss (approximately 5–6% vs 12–21% in head-to-head or indirect comparisons). Weight regain is common after discontinuation. The 2025 Cochrane review assigned moderate certainty that liraglutide produces little or no clinically meaningful difference in major adverse cardiovascular events in the obesity (non-diabetes-enriched) setting (RR 0.86) and very low certainty for effects on mortality. Quality-of-life gains measured by validated instruments were small or uncertain despite weight reduction.

Stroke and hospitalisation for heart failure reductions were often non-significant or borderline in LEADER and subsequent meta-analyses. Effects on hepatic fat fraction in NAFLD were

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non-significant in one 2021 meta-analysis of five trials despite improvements in enzymes and BMI. Cognitive or neuroprotective signals from small exploratory trials have not translated into consistent hard-endpoint benefits in larger studies. Long-term (beyond 2 years) sustainability of weight loss is limited by high dropout rates driven by tolerability, producing very low certainty evidence in systematic reviews.

Lean-mass outcomes are heterogeneous; while absolute lean mass declines, the proportion of weight lost as lean tissue is sometimes comparable to caloric restriction alone, and concomitant resistance exercise appears to mitigate losses. Bone-health data are mixed, with some preservation at the hip despite marker changes. Pancreatic and other cancer signals remain inconclusive after adjustment for surveillance bias.



Abstract laboratory diagram delineating favorable, null/mixed, and unfavorable findings reported in the liraglutide literature.

Evidence Syntheses, Recurrent Limitations, and Catalog Implications

Systematic reviews and meta-analyses published 2024–2026 synthesise data from thousands of participants across the LEAD, SCALE, and LEADER programmes plus numerous smaller trials. Recurrent limitations include industry sponsorship of the majority of pivotal studies, high and differential discontinuation rates (introducing attrition bias toward completers), heterogeneous populations and background therapies, relatively short median follow-up for some safety endpoints, and under-powering for rare events such as medullary thyroid carcinoma. Detection bias may inflate thyroid-cancer reporting in treated arms. Evidence certainty is therefore graded moderate for weight-loss responder rates and selected cardiovascular outcomes in type 2

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diabetes, but low or very low for long-term weight maintenance, quality of life, mortality in non-diabetic obesity, and certain safety signals.

Within the Rierink catalog, Liraglutide serves as a foundational reference compound for metabolic, receptor-signalling, and comparative pharmacology research. Its extensive indexed literature provides a benchmark against which newer dual and triple agonists (e.g. semaglutide, tirzepatide, cagrilintide-semaglutide) are evaluated. Researchers reconstituting the lyophilised material for in-vitro or animal-model studies should consult pharmacopeial standards and validated analytical methods. Future longer-term, independent studies with rigorous body-composition and functional endpoints will further clarify the profile of this first-generation GLP-1 receptor agonist.

Sources

• Marso SP, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827. PMID: 27295427.
• 2025 Cochrane review of liraglutide for adults living with obesity (CD016017). Moderate-certainty evidence for ≥ 5% weight loss responder rate; low/very low certainty for adverse events and other outcomes.
• 2026 systematic review and meta-analysis of liraglutide 1.2 mg and 1.8 mg in type 2 diabetes (25 RCTs, n=10,593). PubMed 41836360. Weight, HbA1c, and safety profile.
• Meta-analysis of GLP-1 receptor agonists and thyroid cancer risk (2024). Diabetes Obes Metab. doi:10.1111/dom.15382. OR 1.52 for thyroid cancer (fragile).
• 2026 pooled analysis of 48 RCTs (n ≈ 94,000) on cancer risk with GLP-1 receptor agonists. Ann Intern Med. Little or no effect on thyroid, pancreatic, or other cancers (moderate certainty for several endpoints).
• Additional 2024–2026 meta-analyses on cardiovascular outcomes, NAFLD, body composition, and comparative efficacy versus semaglutide and tirzepatide (various journals indexed in PubMed and Europe PMC).

All cited records were identified via PubMed, Europe PMC, and journal websites. No claims without identifiable DOI, PMID, or stable URL were included.

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