ClinSphere Journals
International Peer-Reviewed Open Access Journal
Advancing Healthcare, Clinical Research & Innovation
DOI: 10.5281/zenodo.23854944

Review Article

Dual and Triple Incretin Receptor Agonists in Metabolic Disease: Mechanisms, Clinical Evidence, Safety, and Future Perspectives

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Acknowledgments: None.

ABSTRACT

Background: Double glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor stimulation by tirzepatide and the development of triple GIP/GLP-1/glucagon receptor modulation by retatrutide are the latest additions to the category of incretin-based therapies for type 2 diabetes (T2D), obesity and other cardiometabolic conditions.

Objective: Here is the objective to critically understand the mechanisms of both hormones, their clinical usage, therapeutic benefits, possible side effects and the role of pharmacy practice from an Indian perspective.

Methods: A descriptive account of a study; in Section 5 the authors have clearly explained their methodology, search strategy and its disadvantages. Findings: A major feature of tirzepatide is the fact that it brings about larger glycaemic and weight reductions in head-to-head trials compared to GLP-1 RA's semaglutide and dulaglutide. In T2D with advanced atherosclerotic disease, tirzepatide was no inferior to dulaglutide for major adverse cardiac events. Obesity-related heart failure, which is associated with preserved ejection fraction (HFpEF), and reduced apnoea severity were all improved by it. In a steatohepatitis (NASH) phase 2 trial, it also improved histology in the liver. Retatrutide achieved significant phase 2 and phase 3 weight reductions but is still not a FDA approved drug due partly to gastrointestinal adverse effects at the top doses and a high rate of discontinuation for this reason, and to the absence of outcome or safety data. Gastrointestinal side effects, the need for gradual increase of the dosage (dose-titration), the risk of drug-drug interactions, cost and availability are the prime constraints from a practical viewpoint.

Conclusions: In the opinion of the authors, both medicines should be seen as a complement, or part of a wider, coordinated care programme lasting many, or a whole life time where a clinical pharmacist helps with choosing the patient, dose titration, giving patient education, making sure patient remains loyal to therapy, monitoring adverse effects, and designing affordable drug regimen. Comparing one drug with another only based on trial results, and claiming that one is superior to others should be avoided, unless there is direct evidence of better results in head-to-head comparisons. Long-lasting safety, outcome of treatment and actual use of the medications in India are what remain as major gaps in the existing data.

Keywords: Tirzepatide; retatrutide; incretin; GIP; GLP-1; glucagon receptor; type 2 diabetes; obesity; MASLD/MASH; clinical pharmacy; pharmacovigilance; India

1. Introduction

Cardiometabolic disease in India is a big challenge for public health, as national surveys show that more than 100 million patients have diabetes already, while many more suffer from generalised or abdominal obesity, prediabetes, and hypertension[1]. Medication therapy based on incretins has revolutionised treatment first by GLP-1 receptor agonists, which can lower glucose as well as promote weight decrease. Some products can also have cardiovascular and kidney benefits[2]. The development continues with combination of gut- and pancreas-related hormone pathways. Tirzepatide is an once-per-week GIP/GLP-1 receptor co-agonist, available in many jurisdictions for T2D, as well as under separate labelling, for chronic weight management and other indications;[3] retatrutide, a GIP/GLP-1/glucagon receptor agonist, has completed its principal phase 3 obesity readouts, with the first full phase 3 publication appearing in September 2026, but is not yet approved.[4] This review paper presents mechanism, data, safety, and barriers related to clinical use, identifies the findings that are definite versus those under study, and underlines the clinical pharmacists' role.

2. Background

2.1 Incretin physiology

The incretin effect - the enhancement of insulin release that oral glucose causes in comparison to intravenous is primarily the work of two hormones: GIP and GLP-1. The former is secreted by K-cells of duodens, while the latter by L-cells of ileum and colon.[5-7] Besides both stimulating insulin secretion glucose-dependently, GLP-1 can also inhibit glucagon, delay gastric emptying and affect hypothalamic and brainstem circuits thereby decreasing appetite. GIP receptors are expressed,

apart from the classical role in regulating glycemia by modulating secretion of insulin (islets), also on tissues such as fat (adipose tissue), bone, and the central nervous system. Nevertheless, the exact mechanisms of GIP's effect on fat, controlling appetite, and alleviating nausea are still being elucidated.[6,7]

2.2 Rationale and pharmacology of dual GIP/GLP-1 agonism

Tirzepatide is an 39-amino-acid long peptide molecule derived from the GIP sequence that has further been conjugated with a C20 fatty diacid that acts to bind albumin and facilitates once-weekly administration. In vitro, the compound exhibits uneven co-agonism characteristics; the effect on the GIP receptor is similar to that of the endogenous GIP and GLP-1 receptor activity is much lower than endogenous GLP-1.[8]

Possible synergistic mechanisms suggested are more effective insulin secretion and insulin sensitivity, reduction of appetite, and beneficial effects on adipose tissue; however, it is still unclear why dual receptor activation is superior to selective GLP-1 receptor stimulation. Moreover, it is also not clarified by mechanistic means why GIP receptor activation and antagonism can both produce weight loss in in vivo and clinical trials.

Pharmacokinetics as described: Bioavailability after subcutaneous injection is approximately 80%, absorption and onset of action take 8 to 72 hours, elimination half-life is about 5 days, the main metabolic pathways are proteolysis and beta-oxidation with no dose adjustment required for age, sex, or hepatic or renal impairment as per the label.[3]

2.3 Triple GIP/GLP-1/glucagon agonism

Retatrutide provides glucagon-receptor (GCGR) agonism along with GIP and GLP-1 activity.[9] It is believed that glucagon-receptor activation can enhance energy consumption and liver lipid oxidation, and at the same time it may reduce liver fat. On the other hand, GLP-1/GIP activity helps to moderate glucagon's tendency to increase blood sugar. Retatrutide has a dosing frequency of once a week (half-life ≈6 days, from first-in-human data) with in vitro experiments also showing that while it activates the GIP receptor quite effectively, it produces only a very small amount of GCGR stimulation compared to native glucagon.[9] Glucagon-related effects on heart rate and amino-acid metabolism are still under observation and monitoring.

3. Current Evidence

3.1 Type 2 diabetes (established – tirzepatide)

Tirzepatide doses of 5, 10 and 15 mg were found to be not only noninferior but also superior to semaglutide in terms of reducing HbA1c levels, based on metformin background treatment lasting 40 weeks in SURPASS-2. In addition, the weight loss advantage over semaglutide was 1.9, 3.6 and 5.5 kg respectively. The major side effects were of the gastrointestinal system, and serious adverse events were observed in 5 -7% (tirzepatide) compared with 3% (semaglutide).[10] In SURPASS-4, the treatment group of patients at high cardiovascular risk were treated with insulin glargine, and tirzepatide was effective in both HbA1c reduction and weight loss. An exploratory four-point MACE hazard ratio was shown to be 0.74 (95% CI 0.51 - 1.08).[11] The limitations include open-label design, use of different dosages among comparator groups, and sponsor-supported studies.

3.2 Obesity (established – tirzepatide)

In SURMOUNT-1, among adults who were obese without diabetes, and for a period lasting 72 weeks, the average weight change was about -15.0%, -19.5% and -20.9% in the 5, 10 and 15 mg groups respectively, whereas, the placebo group showed a weight change of about -3.1%.[12] In SURMOUNT-5 the head-to-head phase 3b trial with open labels (n=751, 72 weeks), tirzepatide (up to 10 or 15 mg maximum tolerated) resulted in -20.2% versus -13.7% with semaglutide (1.7 or 2.4 mg), and there was reduction in waist-circumference by more in case of tirzepatide (-18.4 vs -13.0 cm) than with semaglutide; it might be worth mentioning, though, that these trials were also open-label and they used a dose approach that was maximally tolerated for the patients.[13] With adults living obese having moderate-to-severe obstructive sleep apnoesa SURMOUNT-OSA tirzepatide led to reduction of apnoea–hypopnoea index by approximately 25–29 vs placebo at 5 events/h.[14]

3.3 Cardiovascular outcomes

SURPASS-CVOT (n=13,299; T2D with established atherosclerotic cardiovascular disease; median follow-up approx.4 years) studied tirzepatide versus dulaglutide 1.5 mg and the primary composite (cardiovascular death, myocardial infarction, stroke) happened 12.2% vs. 13.1% (HR 0.92; p=0.003 for non-inferiority and p=0.09 for superiority), and with tirzepatide more HbA, higher weight loss and worse gastrointestinal adverse effects.[15] This result supports cardiovascular safety and offers benefits comparable, at least, to a drug with proven outcomes, but it provides no evidence of superiority, and there is no comparison with a placebo. In SUMMIT (HFpEF with obesity), tirzepatide decreased cardiovascular death or worsening heart failure as a composite (HR 0.62) and also enhanced health status scores.[16] A specific trial on obesity (in the realm) of mortality/morbidity (SURMOUNT-MMO) has been registered as currently ongoing, verification of the status is required.

3.4 Kidney outcomes

The results of the SURPASS-4 post hoc analysis showed that tirzepatide treatment was related with a slower rate of decline in eGFR and a lower level of albuminuria compared to glargine.[17] This dataset is purely hypothesis-generating while the top-rated evidence regarding kidney outcome from a GI hormones perspective comes currently as a result from semaglutide (FLOW)[18] and the authors advise checking the dedicated tirzepatide kidney-outcome data at the time of submission. Recommended primary therapy for chronic kidney disease, renin--angiotensin system blockade plus SGLT2 inhibitors, remains intact.

3.5 MASLD/MASH

In theSURPASS-3MRI substudy, tirzepatide significantly reduced liver fat and the volumes of visceral and subcutaneous adipose tissues compared to insulin degludec.[19] In phase 2 SYNERGY-NASH trial patients (52 weeks, biopsy-confirmed MASH with F2-F3 fibrosis), the resolution of MASH was

without worsening fibrosis in 44%, 56% and 62% after taking the 5 mg, 10 mg and 15 mg dose respectively, whereas only about 10% of participants in the placebo group had similar outcomes.[20] The small sample size and short duration of phase 2 trials as well as the use of histologically-based surrogate endpoints do not allow one to draw reliable conclusions about liver cirrhosis or liver-related outcomes; resmetirom already has phase 3 histological evidence,21 and the recommendations (AASLD) are mainly around lifestyle intervention, cardiometabolic risk management and fibrosis risk stratification.[22]

3.6 Retatrutide (investigational)

Phase 2: in adult patients with obesity (48 weeks), the compound retatrutide led to dosage-dependent reduction in weight up to about 24 % at 12 mg;[23] it also resulted in significant decreases of HbA1c and fat weight in T2D which even surpassed the effects of dulaglutide;[24] and it substantially lowered fat in the liver in a MASLD substudy;[25] Phase 3: TRIUMPH-1 (n=2,339; obesity without diabetes; 80 weeks; 4, 9 or 12 mg versus placebo) was published in the New England Journal of Medicine on 29 September 2026;[4] the company's description of the top-line results indicated that the average weight losses were about 28 % at 12 mg among the individuals who remained on treatment (approximately 25% if counting all those assigned to treatment).A higher proportion of patients left the study due to adverse events at 12 mg (around 11%) as compared to placebo (around 5%). Trial topline summaries (TRIUMPH-2 for T2D; TRIUMPH-3 severe obesity plus cardiovascular disease, about 22.6% weight loss) Additional top-line results (TRIUMPH-3 in patients with severe obesity and cardiovascular disease, weight losses up to about 22.6%) came out from the sponsor on 23 July 2026;[26] TRIUMPH-4 (knee osteoarthritis trial) has been registered.[27] Regulatory submission is said by the company to be in early 2027; however, the drug has not been approved yet. Comparing the trials of tirzepatide against other drug is not justified as the features (patient population, duration, target outcome definitions, and how drugs are escalated over time) are all different between the trials.

3.7 Guidelines

Along with GLP-1 RAs, the dual GIP/GLP-1 RA also are mentioned as first-line therapies in the ADA (American Diabetes Association) Standards of Care in Diabetes, 2026 guideline, if weight loss and cardiovascular or kidney risk reduction are top goals.[28] On the other hand, for kidney-targeted therapy, KDIGO Diabetes and CKD guideline should be the one to check. [29]

4. Clinical Applications

- **T2D:** adjunct to lifestyle and metformin (or as monotherapy where appropriate) when substantial HbA1c and weight reduction are desired; useful with basal insulin, with insulin and sulfonylurea doses reduced pre-emptively to limit hypoglycaemia.
- **Obesity / overweight with comorbidity:** chronic weight management as an adjunct to reduced-calorie diet and physical activity, recognising that obesity is chronic and weight regain after discontinuation is common.
- **Cardiometabolic phenotypes:** T2D with ASCVD (non-inferiority to dulaglutide), HFpEF with obesity, obstructive sleep apnoea with obesity (licensed indications vary by country – confirm local labels).
- **MASLD/MASH:** investigational for histological MASH outcomes in many jurisdictions; use is for cardiometabolic indications with liver benefit as a potential co-benefit.
- **Patient selection:** prioritise those with the greatest expected benefit; avoid use for cosmetic weight loss; consider pregnancy planning, history of pancreatitis or gallbladder disease, diabetic retinopathy, eating disorders and surgery plans.

5. Safety & Limitations

Common side effects: nausea, vomiting, diarrhoea, constipation, gastritis, and loss of appetite. The level is mainly mild to moderate and depends on the dosage with symptoms being more prevalent during dose ramp up.[10],[12]

Safety Warnings/Contraindications on the product label: Risk of thyroid C-cell tumours (boxed warning in US; contraindicated for a history of MTC or MEN2 either personal/family history); pancreatitis; biliary disease; hypoglycaemia in those on insulin or insulin secretagogues; dehydration-induced acute renal failure; allergy; severe GI disease caution; retinopathy in DM2 patients, and especially with fast glucose lowering; pulmonary aspiration during anaesthesia or deep sedation as possible complications; pregnancy-related (contraindicated).

Drug interactions: delayed gastric emptying may change absorption of oral medications; the label recommends using additional or non-oral contraception for a period after initiation and after dose increment for individuals on hormonal methods of birth control; Drugs with a Narrow Therapeutic Index should be closely watched.

Others: losing lean mass along with weight loss, food balance, gallstones formation, losing hair, watching out for depression/suicidal thoughts during the treatment, and the signals (e.g., rare ocular events reported with a class of drugs) that require watching out for developments in regulation.

Retatrutide: There are few safety data on this drug, mainly from phase 2/3 trials. The reported side effects were mainly dose-dependent gastrointestinal symptoms, discontinuation increased with maximum dose, and heart rate changes (probably because of glucagon). Some other side effects like dysaesthesia were also noted in the initial phase of development, and we do not know what long-term effects will be.

Limitations of the evidence: mostly funded by the Sponsor; no blinding in the control arms of the studies where both interventions were compared (head-to-head trials) except where mentioned; only patients who fit a narrow range of criteria were included; lack of or very few subjects from India / South Asia which will need quantification from the authors; not much data about how long the effects of the treatment last or information about dropping out of the trial; using proxy endpoints for MASH; and cost-effectiveness data can hardly be generalised to different contexts.

6. Emerging Advances

Tirzepatide-class and retatrutide development also involves different avenues such as: the GLP-1/glucagon co-agonists (survodutide, mazdutide, pemvidutide), amylin-based combinations, oral small-molecule GLP-1 agonists (orforglipron which was granted approval in the US for chronic weight management on 1 April 2026),[30]phase 3 reports like the one from survodutide on obesity and T2D (New England Journal of Medicine 29 September 2026;[31]). Important areas are getting patients used to the dosage so that a maintenance phase is not necessary, preservation of lean mass, combinations of different drugs, indications for children and adolescents, outcome trials in MASH and CKD, and head-to-head trials.

7. Clinical Pharmacy Implications

Clinical pharmacists can contribute across the care pathway (Figure 2; Table 4):

1. **Assessment and eligibility:** screen for contraindications (MTC/MEN2, pancreatitis, pregnancy plans), gallbladder disease, retinopathy status, eating-disorder history and perioperative plans; reconcile all medicines and supplements.
2. **Medication review:** anticipate hypoglycaemia (reduce insulin/sulfonylurea), assess oral drug absorption issues, review hormonal contraception advice, and rationalise antihypertensives and diuretics when weight, appetite and fluid intake change.
3. **Counselling:** injection technique (pen storage, rotation, missed-dose rules per product label), slow titration, small frequent meals, hydration, recognising pancreatitis/gallbladder/dehydration red flags, and realistic expectations of weight loss and plateau.
4. **Adherence and persistence:** address cost, supply gaps, injection anxiety and tolerability; plan for weight regain after discontinuation; coordinate review at each escalation.
5. **Adverse drug reaction (ADR) reporting:** report suspected ADRs, product-quality concerns and counterfeit/substandard products to the Pharmacovigilance Programme of India (PvPI) and the local regulator. [32]
6. **Interprofessional collaboration:** co-management with endocrinologists, cardiologists, nephrologists, hepatologists, dietitians and primary care; protocol-based dose titration and shared documentation.
7. **Medication safety:** counsel against unregulated compounded or imported "research-grade" peptides; verify supply source; avoid duplication of GLP-1 RA therapy.

Indian healthcare context. Affordability is one of the key issues (original tirzepatide is significantly more expensive even than the most generic diabetes drugs and generic semaglutide which will be introduced after patent expiry around 2026; prices and market data should be double checked), besides lack of coverage by insurance, specialist services not available equally in different areas, possibility of self-medication or use of fake/counterfeit drugs, low health-reading skills population, vegetarian/local dietary advice, difficulties in adverse reactions reporting/collecting. Community and hospital pharmacists can help with the appropriate and rational use of medicines by identifying high-risk individuals or groups for medicine misuse or overdose, informing patients about possible alternatives that are safer and have similar effects, and initiating community/regional registries or audit programmes through collaborations.

7.1 Pharmacovigilance and safety signals relevant to practice

Trials at class level for incretins reveal an increased risk of gallstones (cholelithiasis) and other disorders of the biliary tract, while the association of pancreatitis and pancreatic cancer is far less clear.[33-34] Observational studies suggest GLP-1 RA usage to aid with weight loss is strongly indicated in occurrence of gastrointestinal incidents, which include pancreatic inflammation, delayed stomach empting (gastroparesis), and blockage of intestine (bowel obstruction); though confounding by indication is a limitation.[35] Semaglutide is among the few GLP-1 RAs where residual gastric content has been identified through upper endoscopy in the literature,[36] and pharmacists should follow current guidelines for medication use around operations since recommendations are constantly updated;[37] Rare sight-threatening cases of ischaemic optic neuropathy in absence of retinal artery occlusion (non-arteritic anterior ischaemic optic neuropathy-NAION) were found in a retrospective analysis for semaglutide,[38] but evidence from similar cases involving tirzepatide and retatrutide is very minimal. An extensive study showed that using a GLP-1 RA (seamaglutide) was associated with the same chance of causing suicidal thoughts as were comparator antidepressants, which would be another strong indicator for the psychiatric side effects of these medications and monitoring should be done. The findings for cancer of the thyroid gland in the context of GLP-1 RAs are inconclusive; while one large national study pointed out that there was a rise in risk with a longer time exposed, the real risk is probably very low and there were possible residual biases, the contra-indication (label warning) to use in the presence of thyroid carcinoma has not been rescinded.[40]

Changes in microangiopathy such as retinopathy were associated with HbA1c level fluctuations when patients treated with semaglutide had marked decreases in blood sugar levels, which supports the importance of eye tests before and during diabetes management with this medicine intensification.[42] Suspected adverse drug reactions are the way in which pharmaceutical regulatory systems monitor for unexpected harmful effects of medicines; a network to monitor adverse effects on patients taking pharmaceuticals (PvPI) in India and how its development as well as reporting process has been done are described here[42]; When adverse drug reactions (ADR) are reported by a pharmacist, it should contain information of the medication used, lot number, strength, time between administration and onset of symptoms, any other medications taken along with it, as well as what finally turned out to the patient.

7.2 Adherence, persistence and pharmacist-led care

Non-compliance with long-term treatment is common worldwide. About 50% of patients in high-income countries do not use prescribed chronic medications.[43] Cochrane review suggests that the most helpful adherence interventions usually

involve multi-component approaches, and even then, the effect is small.[44] Systematic reviews have pointed out that pharmacist initiated programmes can lead to improvement of glycaemic control and adherence among diabetic adults[45-46] as well as the improvement of cardiovascular risk factors.[47] Pharmacokinetics real-world data on the use of GLP-1 RA for weight loss in patients without diabetes, showed considerable dropout already within the first year,[48] hence highlighting the necessity of structured follow-up regarding dose escalation, tolerability, and cost. Pharmacist-delivered programmes specific to tirzepatide or retatrutide have not been studied yet and could be a research gap (Section 12).

7.3 Additional Indian and South Asian considerations

India is home to some of the largest number of people who are suffering from diabetes across the world.[49] South Asians tend to develop type 2 diabetes at younger ages and with lower body-mass index than white Caucasian populations.[50] Asian-specific BMI and waist-circumference thresholds have been suggested as the best way to determine intervention at an earlier stage.[51-52] Results of a national survey showed increasing overweight and obese population[53] and pooled global analytical results demonstrated that the number of diabetes-related deaths is going up and there is a massive treatment gap yet.[54] The SURPASS-AP-Combo trial is a comparison between tirzepatide and insulin glargine in Asia-Pacific participants.[55] Indian-specific efficacy studies on this drug are required. Also, there is a need for studies on how effective the use of this drug will be in terms of persistence and cost-effectiveness among the Indian population. Affordability, reimbursement and product-quality assurance are key areas for pharmacist-led stewardship.

8. Research Gaps

1. Placebo-controlled cardiovascular and kidney outcome trials for tirzepatide in non-diabetic obesity and CKD.
2. Long-term (>3–5 year) safety, durability, withdrawal and weight-regain data, including lean-mass and bone outcomes.
3. Histological-to-clinical outcome linkage in MASH; cirrhosis populations.
4. Retatrutide outcome and safety data, optimal maintenance dosing and glucagon-related effects.
5. Representation of South Asian populations, who develop T2D at lower BMI; Indian real-world effectiveness, persistence and cost-effectiveness.
6. Pharmacist-led intervention trials (adherence, ADR detection, glycaemic/weight outcomes, cost).
7. Pharmacovigilance signal detection (pancreatic, biliary, ocular, psychiatric, pregnancy exposure) in routine practice.

Context from related programmes. Benchmarks set by semaglutide and dulaglutide outcome trials (SUSTAIN-6,[56] SELECT,[57] REWIND[58]) remain the standard against which placebo-controlled outcome evidence for tirzepatide in obesity will be judged. Weight regain after stopping treatment is well documented: about two-thirds of lost weight was regained one year after semaglutide withdrawal in the STEP 1 extension,[59] and in SURMOUNT-4 switching from tirzepatide to placebo led to weight regain whereas continued treatment produced further loss,[60] Supporting studies are currently ongoing of research focusing on maintenance dose and long-term strategies. In patients with both heart failure with preserved ejection fraction and metabolic associated fatty liver disease (MASH), semaglutide shows randomised evidence (STEP-HFpEF,[61] and ESSENCE[62] studies), however head-to-head trials between tirzepatide are lacking; therefore, to be safe we need to rely indirectly on comparison studies, and for guidance in terms of patient management during this interims period we may be referred, for example, to recommendations such as those of the EASL, EASD, EASO MASLD guideline[63]. Additionally, in line with clinical definitions of obesity that involve organ impairment or dysfunction, such approaches may be helpful for selecting patients to start with pharmacotherapy.[64]

9. Future Perspectives

The ability of multi-receptor agonism to change obesity treatment in the direction of outcome-driven, phenotype-based care is such that a drug's selection is based on an individual's comorbidity (HFpEF, OSA, MASH, CKD) rather than weight loss alone may be a possibility. Development trends are supposed to involve oral and infrequent doses, maintenance therapies, combination drug treatment, and generic drugs that might be competitive in India. Pharmacist pathways, registries and affordability plans would help in making sure the health systems provide the greatest benefit to the most burdened populations. Anti-obesity drug discovery reviews predict that multi-agonist and combinational treatment methods will come next;[65] phase I-II clinical trials of the retatrutide drug have shown heart rate effects; the results should be monitored as glucagon-receptor agonist drugs get developed through clinical phases;[66] meanwhile, the GLP-1/glucagon co-agonist survodutide has phase 2 data in obesity[67] and MASH, [68], and such data highlight the fact that glucagon-receptor agonism is being tried for hepatic indications.

10. Conclusion

Dual GIP/GLP-1 agonism with tirzepatide is an established, evidence-supported option for T2D and obesity, with head-to-head superiority over semaglutide and dulaglutide for glycaemic and weight outcomes, cardiovascular non-inferiority to dulaglutide, and encouraging data in HFpEF, OSA and MASH. Triple agonism with retatrutide is promising but investigational. Clinical benefit depends on careful selection, titration, safety monitoring and sustained support – areas in which clinical pharmacists are well placed to lead. Claims of superiority should be restricted to head-to-head evidence, and long-term safety and Indian real-world data remain priorities

Tables and Figures

Table 1. Dual and triple incretin-based agents and receptor targets

Agent	Receptor targets	Status (verify at submission)	Notes
Tirzepatide	GIPR + GLP-1R (GIPR-weighted co-agonist)	Approved (T2D; chronic weight management and other indications vary by country; confirm CDSCO status)	Once-weekly SC; C20 fatty diacid; t½ ≈5 days
Retatrutide	GIPR + GLP-1R + GCGR	Investigational; four TRIUMPH phase 3 readouts reported (sponsor); no approval reported as of 17 Oct 2026 [VERIFY]	Once-weekly SC; t½ ≈6 days [K]
Survodutide	GLP-1R + GCGR	Investigational; phase 3 in obesity/MASH	Dual agonist; not GIP-based
Mazdutide	GLP-1R + GCGR	Regulatory status in China to be verified	Listed for context
Pemvidutide	GLP-1R + GCGR	Investigational (MASH)	Listed for context

Table 2. Major clinical trials

Trial	Population / comparator	Duration	Principal findings
SURPASS-2	T2D on metformin; tirzepatide 5/10/15 mg vs semaglutide 1 mg	40 wk	Superior HbA1c; extra weight loss 1.9/3.6/5.5 kg; GI events predominant
SURPASS-4	T2D, high CV risk; vs glargine	up to ~2 y	Greater HbA1c and weight reduction; exploratory MACE-4 HR 0.74 (0.51–1.08)
SURPASS-CVOT	T2D + ASCVD, n=13,299; vs dulaglutide 1.5 mg	median ≈4 y	MACE-3 12.2% vs 13.1%; HR 0.92; non-inferior (p=0.003), superiority not shown (p=0.09)
SURMOUNT-1	Obesity, no diabetes; vs placebo	72 wk	−15.0/−19.5/−20.9% vs −3.1%
SURMOUNT-5	Obesity, no diabetes, n=751; vs semaglutide (open-label)	72 wk	−20.2% vs −13.7%; waist −18.4 vs −13.0 cm
SURMOUNT-OSA	Obesity + moderate–severe OSA	52 wk	AHI reduction ≈25–29 vs ≈5 events/h [VERIFY]
SUMMIT	HFpEF + obesity	median ≈2 y	Reduced CV death/worsening HF (HR ≈0.62) [VERIFY]
SYNERGY-NASH (ph 2)	MASH, F2–F3	52 wk	MASH resolution ≈44/56/62% vs ≈10% placebo [VERIFY]
Retatrutide ph 2 (obesity)	Obesity ± overweight, no diabetes	48 wk	up to ≈24% weight loss at 12 mg
TRIUMPH-1 (ph 3)	Obesity, no diabetes, n=2,339	80 wk	≈25% (all randomised) to ≈28% (adherent) at 12 mg vs placebo ≈2–4% [VERIFY estimands]
TRIUMPH-2/-3 (ph 3, topline)	**T2D + obesity; severe obesity + CVD**	**80 wk**	**Primary endpoints met per sponsor; up to ≈22.6% (TRIUMPH-3)**

Table 3. Comparative efficacy and safety

Domain	Tirzepatide	Retatrutide (investigational)	Semaglutide / dulaglutide (reference)
Mechanism	GIPR/GLP-1R	GIPR/GLP-1R/GCGR	GLP-1R
Head-to-head evidence	Superior glycaemia/weight vs semaglutide (SURPASS-2, SURMOUNT-5); CV non-inferior to dulaglutide	None vs approved comparators in phase 3 [VERIFY]; phase 2 vs dulaglutide in T2D	Comparators in the trials above
CV outcomes	Non-inferior vs dulaglutide; HFpEF benefit (SUMMIT)	Not yet reported	Placebo-controlled MACE/HF/kidney data for semaglutide and dulaglutide
Kidney	Post hoc signals only	Not established	FLOW (semaglutide)
GI tolerability	Dose-related; discontinuation lower in SURMOUNT-5 (2.7%) vs semaglutide (5.6%)	Higher GI-related discontinuation at 12 mg (≈11% vs ≈5% placebo) [VERIFY]	Dose-related GI events
Formulation	Weekly SC pen / vial (varies by country)	Weekly SC (investigational)	Weekly SC; oral semaglutide available
Interpretation	Established	Investigational; long-term safety unknown	Established

Phase	Parameters	Pharmacist intervention
Baseline	History (MTC/MEN2, pancreatitis, gallstones, retinopathy, eating disorders), pregnancy plans, medicines, HbA1c, weight/BMI, waist, BP, renal function (eGFR, UACR), liver tests/FIB-4, lipids	Eligibility screen; reconcile medicines; pre-emptive insulin/sulfonylurea reduction; contraception counselling
Initiation / each escalation	GI symptoms, hydration, appetite, glucose logs/hypoglycaemia, injection technique	Teach pen use, storage, missed doses; small frequent meals; hydration; escalate no faster than label allows; reassess oral drug absorption
Ongoing (3–6 monthly)	Weight, HbA1c, BP, renal function, liver markers, lean-mass/nutrition, mood, visual symptoms	Adherence/persistence review; ADR screening; nutritional adequacy; coordinate retinal screening
Red flags	Persistent severe abdominal pain, vomiting/dehydration, right-upper-quadrant pain, neck mass/dysphagia, vision change, hypersensitivity	Urgent referral; stop pending review; report to PvPI
Peri-procedural	Planned surgery/sedation	Alert anaesthesia team; follow current institutional guidance on GLP-1/GIP agonists [VERIFY]
Access	Out-of-pocket cost, supply, counterfeits	Cost counselling; verify supply chain; advise against unregulated peptides

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