

“VerSemaglutide”: The Versatile Semaglutide

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Background & Aim

- Semaglutide, a GLP-1 receptor agonist, is now central to the T2DM management, obesity, and CV risk, with emerging benefits in MASLD, CKD, and obesity-related cancers.
- With injectable semaglutide patents expiring from 2026 (including in India), access through generics is expected to rise. This review summarizes evidence from 2016–2025 across diverse patient populations including both oral and injectable dosage forms.

Material & Methods

- We reviewed phase 3 trials and beyond, including but not limited to SUSTAIN, PIONEER, SOUL, etc.
- Populations studied (N: ~1.4 lacs) included T2DM, obesity/overweight, obesity-related cancers, renal impairment, MASLD, and CVDs.
- Key outcomes were HbA1c, weight loss, MACE, liver histology, kidney function, cancer incidence, and safety.

Table 1: Semaglutide's effectiveness and safety across various patient profiles

Trial	Form.	Disease Area	N	Major Findings	Safety Profile
SUSTAIN 1 to 5, 7, 6		T2DM, Overweight/Obesity, CV Risk	~9,000	Significant HbA1c ↓1.2–1.8%, weight loss 7–12%, 26% ↓MACE	Gastrointestinal (GI) symptoms common; rare pancreatitis
PIONEER 1-8, SOUL		T2DM, CV Risk	~10000, ~9000	Significant HbA1c & weight reduction; 14% ↓MACE (SOUL)	GI symptoms common; low hypoglycaemia risk
STEP 1-8, STEP TEENS		Obesity & Overweight	>5,000	Up to 15% weight loss maintained to 4 years; effective and safe in adolescents	GI symptoms common; cholelithiasis
SELECT		CV Outcomes in Overweight/Obese w/o Diabetes	17,604	20% ↓ MACE & 8.5% weight loss vs placebo	GI symptoms common; increased discontinuations at lower BMI
STEP UP		Obesity	1,407	Semaglutide 7.2 mg resulted in 20.7% average weight loss; 33% achieved >25% weight loss.	Safety/tolerability comparable to 2.4 mg; GI symptoms common
ESSENCE		MASLD/MASH with Fibrosis	534	Steatohepatitis resolution in 63% patients, fibrosis regression in 37% patients, 10.5% weight loss	GI symptoms common
FLOW		CKD with T2DM	3,800	22% ↓ kidney failure progression or CV death; slowed eGFR decline, death	Consistent safety; GI symptoms common
STRIDE		Peripheral Artery Disease with T2DM	792	↑ walking distance, quality of life, ↓ disease progression	Serious GI events (~1%)
Cohort Study (Cancer risk)		Obesity-related Cancers	>85,000	↓ cancer risk: 47% ovarian, 25% endometrial & 31% meningioma	Kidney cancer risk (non-significant)

Results

- Semaglutide reduces HbA1c, body weight, MACE, adverse kidney outcomes and certain obesity-related cancers.
- Emerging evidence includes STEP HFpEF trial (significant improvement in KCCQ-CSS score in HFpEF), early evidence in **obstructive sleep apnoea** improvement, benefits in **PCOS**, **male obesity-related infertility (sperm morphology, testosterone, hypogonadism)**.
- Ongoing phase 3 EVOKE and EVOKE+ trials are also evaluating its potential in **Alzheimer's disease**.

Conclusion

Semaglutide has progressed from a diabetes drug to a versatile therapy with broad systemic benefits. It exemplifies the potential of a single molecule to cross traditional disease boundaries and reshape holistic management in metabolic and related disorders.

Declaration

Authors declare no conflict of interest.

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