

ORIGINAL RDNA SEMAGLUTIDE IN THE CARDIOVASCULAR-KIDNEY-LIVER-METABOLIC (CKLM) CONTINUUM: BRIDGING CLINICAL EFFICACY AND PUBLIC HEALTH VALUE IN INDIA

Cardiology

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ABSTRACT

The American Heart Association's cardiovascular-kidney-metabolic (CKM) syndrome framework treats cardiovascular disease, chronic kidney disease (CKD), and metabolic dysfunction as one adiposity-driven continuum. A growing evidence base now extends this to a cardiovascular-kidney-liver-metabolic (CKLM) continuum that includes the liver. Original rDNA semaglutide is the only GLP-1 receptor agonist with dedicated outcomes evidence across this whole continuum: durable weight loss in the STEP programme, a 20% reduction in major cardiovascular events (SELECT), a 24% reduction in major kidney events (FLOW), resolution of steatohepatitis (ESSENCE), and additional benefit in heart failure, peripheral artery disease, knee osteoarthritis, and possibly Alzheimer's risk. This rests on more than 49 million patient-years of exposure and over 50 clinical trials. India's core semaglutide patent expired in March 2026, and domestically manufactured synthetic-route generics have since entered the market. This review sets that evidence base against India's disease burden and examines the manufacturing and regulatory questions, that shape how original and synthetic semaglutide should be weighed in Indian clinical and policy decisions.

KEYWORDS

Semaglutide; Cardiovascular-Kidney-Liver-Metabolic (CKLM) Syndrome; GLP-1 Receptor Agonists; Regulatory and Manufacturing Considerations.

INTRODUCTION

Cardiovascular disease, chronic kidney disease, and metabolic disorders such as type 2 diabetes and obesity were long managed as separate problems, each with its own specialty and guideline. In 2023, the American Heart Association proposed cardiovascular-kidney-metabolic (CKM) syndrome: a single continuum driven by dysfunctional or excess adiposity, staged from 0 to 4.[1] A 2026 joint guideline from the AHA, ACC, ADA, and ASN turned this into formal clinical practice.[2] More recent literature extends the same logic to the liver, describing a cardio-kidney-liver-metabolic (CKLM) spectrum in which metabolic dysfunction-associated steatohepatitis (MASH) sits alongside cardiovascular and renal disease as a downstream consequence of the same adiposity-driven process.[3]

Original rDNA semaglutide is the clearest test of this idea in practice. It is the only GLP-1 receptor agonist with dedicated, large-scale outcomes trials across every domain of the CKLM continuum: the STEP programme for weight, glycaemic outcomes across the SUSTAIN and PIONEER programmes, SELECT for cardiovascular outcomes, with SUSTAIN-6 and the SOUL trial providing further cardiovascular evidence in type 2 diabetes, FLOW for kidney outcomes, and ESSENCE for MASH, with further dedicated evidence in heart failure, peripheral artery disease, and osteoarthritis.[4–10] More than 49 million patient-years of real-world exposure and over 50 completed clinical trials sit behind original rDNA semaglutide.[3]

India adds a distinct dimension to this picture. The country carries one of the world's largest burdens of CKLM-relevant disease, and its core semaglutide patent expired in March 2026.[11,12] Domestically manufactured synthetic-route copies entered the market within weeks, which has understandably framed the Indian conversation around affordability.[3,13] This review takes a different starting point. Rather than asking how access can be widened at the lowest price, it asks what has actually been demonstrated for each manufacturing route, and what public health value that evidence represents, quite apart from the price question.

This review has four aims: to summarise the trial evidence for original rDNA semaglutide across the CKLM continuum, including hepatic, musculoskeletal, and cognitive domains beyond the cardio-renal-

metabolic core; to set that evidence against India's disease burden; to examine, using the peptide-manufacturing and regulatory literature, why original rDNA semaglutide's production route and the synthetic routes used by most generics are not interchangeable by default; and to demonstrate that evidence rather than label similarity should anchor clinicians and policymakers in India to weigh original rDNA semaglutide against synthetic copies.

The CKM/CKLM Syndrome and burden in India

The AHA's 2023 advisory defines CKM syndrome as a progressive, multiorgan state in which excess or dysfunctional adiposity drives metabolic risk factors (dysglycaemia, hypertension, dyslipidaemia), which in turn drive CKD and cardiovascular disease.[1] Its staging system, runs from Stage 0 (no risk factors) to Stage 4 (established cardiovascular disease), built for prevention across the life course rather than only treatment after damage occurs.[1,2]

The staging thresholds for BMI, eGFR, and albuminuria come mostly from Western cohorts, yet South Asian, Chinese, and other Asian populations develop central adiposity and cardiometabolic risk at lower BMI thresholds than White European cohorts. That is why NICE and related guidelines recommend lower cut-offs for these populations: overweight at 23–27.4 kg/m² and obesity from 27.5 kg/m². [14,15] The framework's own logic also calls for early, upstream treatment, before Stage 3–4, which places therapies with the broadest and most reliable evidence base. Early, preventive use is precisely where an unproven substitution would be hardest to catch clinically before harm is done India faces a substantial CKLM burden. The ICMR-INDIAB study of more than 113,000 people estimated 101 million adults with diabetes and 136 million with prediabetes, alongside high rates of hypertension and obesity.[11] CKD affects roughly 16% of the population and is strongly associated with diabetes and hypertension.[12] Together, these overlapping conditions place a very large population at risk of progressing through CKM stages 2 and 3. Much of this burden falls on public healthcare purchasers, including the Central Government Health Scheme, the Employees' State Insurance Scheme, the Defence Services, the Railways, and state government health programmes, which makes the evidence-versus-price question raised in this review directly relevant to how these systems select and reimburse semaglutide products.

Original Semaglutide's Clinical Case Across the CKLM Continuum

The clinical rationale for semaglutide across the CKLM continuum is compelling. Excess adiposity is a key driver of metabolic, renal, hepatic, and cardiovascular disease; therefore, therapies that achieve substantial and sustained weight loss may confer benefits across these interconnected systems. Figure 1 maps the clinical evidence for original rDNA semaglutide across five organ and tissue domains. Comparable clinical outcomes have not yet been demonstrated for synthetic-route semaglutide copies.[3,13]

Original rDNA Semaglutide's Evidence Across the Cardiovascular-Kidney-Liver-Metabolic (CKLM) Continuum

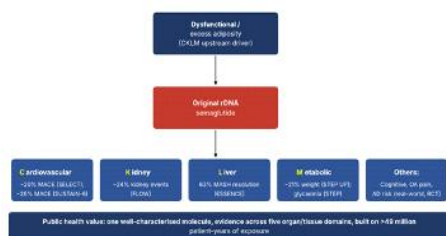


Figure 1. Original rDNA semaglutide's evidence across the cardiovascular-kidney-liver-metabolic (CKLM) continuum.

Metabolic efficacy: the STEP programme

STEP 1 established the weight-loss efficacy of once-weekly subcutaneous semaglutide 2.4 mg in adults with overweight or obesity without diabetes.[4] The STEP UP trial subsequently showed a dose-dependent effect at 72 weeks: mean weight loss of 17.5% with semaglutide 2.4 mg, rising to 20.7% with the higher 7.2 mg dose.[16] Longer-term data from SELECT showed that this effect was sustained, with a mean weight reduction of 10.2% at 208 weeks compared with 1.5% with placebo.[17] Similar findings have been reported in Asian populations. In STEP 6, conducted in East Asian adults with obesity, semaglutide produced a mean weight reduction of 13.2% at week 68 versus 2.1% with placebo, together with a 40.0% reduction in abdominal visceral fat area compared with 6.9% in the placebo group.[18] STEP 11, conducted in South Korea and Thailand, and a real-world Indian study reporting a 14.7% relative weight reduction over six months further support the effectiveness of semaglutide in South and East Asian populations.[19,20]

Cardiovascular efficacy: SELECT and the SUSTAIN/PIONEER pooled analysis

SELECT enrolled 17,604 adults with overweight or obesity, established cardiovascular disease, and no diabetes.[6] Semaglutide reduced the risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 20% compared with placebo (6.5% vs 8.0%; HR 0.80, 95% CI 0.72–0.90).[6] The treatment effect was observed across glycaemic subgroups and was particularly pronounced among Asian participants.[13,21] Cardiovascular benefits also extended to patients with heart failure with preserved ejection fraction in the STEP-HFpEF programme.[22,23] In type 2 diabetes, pooled data from SUSTAIN-6 and PIONEER 6 showed a 24% reduction in major adverse cardiovascular events, with benefits seen across subcutaneous and oral semaglutide formulations and across cardiovascular and CKD subgroups.[5] Together, these trials support cardiovascular benefit with semaglutide across populations with and without diabetes. Real-world evidence points in the same direction: the STEER study found a 57% reduction in major cardiovascular events with semaglutide than with tirzepatide among US adults with obesity and established cardiovascular disease who had no treatment gaps longer than 30 days (29% in the full treated cohort), and the SCORE study reported a larger reduction in cardiovascular events among semaglutide users than non-users than was observed in SELECT.[24]

Renal efficacy: the FLOW trial and REMODEL trial

FLOW, the first dedicated kidney-outcomes trial of a GLP-1 receptor agonist, enrolled 3,533 adults with type 2 diabetes and established CKD.[9] Semaglutide 1.0 mg reduced the risk of the primary kidney composite outcome by 24% and slowed annual eGFR decline by 1.16 mL/min/1.73 m² compared with placebo. It also reduced major cardiovascular events by 18% and all-cause mortality by 20%.[9] These benefits were observed across levels of CKD severity and included a 27% reduction in heart failure events or cardiovascular death, with no additional safety concerns when semaglutide was used alongside an SGLT2 inhibitor.[25–27] REMODEL provided

mechanistic support for these clinical findings. In 106 adults with type 2 diabetes and CKD, semaglutide 1.0 mg for 52 weeks was associated with 40% lower UACR and 12 mL/min higher creatinine clearance versus placebo, together with reductions in perirenal fat (25%) and renal sinus fat (13%). Kidney imaging and biopsy analyses also suggested improved renal haemodynamics and reduced endothelial, inflammatory, and fibrotic injury.[27]

Hepatic efficacy: the ESSENCE trial and real-world MASLD data

ESSENCE demonstrated the hepatic efficacy of semaglutide 2.4 mg in patients with MASH and F2–F3 fibrosis. Steatohepatitis resolved without worsening of fibrosis in 62.9% of patients receiving semaglutide versus 34.3% with placebo, while fibrosis improved without worsening steatohepatitis in 36.8% versus 22.4%, respectively (both $p < 0.001$).[10] These findings have supported an approved indication for non-cirrhotic MASH with moderate-to-advanced fibrosis.[3] Real-world data in MASLD have also shown improvements in liver enzymes and hepatic synthetic function, together with a lower risk of progression to advanced liver disease.[28]

Additional domains: heart failure with preserved ejection fraction, peripheral artery disease, musculoskeletal, and cognitive outcomes

Semaglutide has also shown benefits beyond the core metabolic, cardiovascular, renal, and hepatic domains. The STEP-HFpEF programme demonstrated improvements in symptoms, physical function, and exercise capacity in patients with obesity-related heart failure with preserved ejection fraction.[22,23] In peripheral artery disease, STRIDE showed improved walking capacity in people with type 2 diabetes and symptomatic disease.[29] In obesity with knee osteoarthritis, semaglutide produced a greater reduction in osteoarthritis-related pain than placebo (41.7 vs 27.5 points).[30] Observational data have additionally associated semaglutide use with a lower risk of a first Alzheimer's disease diagnosis than other antidiabetic therapies, although these findings do not establish causality.[31] Oral semaglutide has also demonstrated cardiovascular benefit in high-risk type 2 diabetes in the SOUL trial, with a 27% relative reduction in major adverse cardiovascular events in the Asian subgroup.[7]

Synthesis: one molecule, five organ domains, one manufacturing route

Table 1 brings together the evidence across the metabolic, cardiovascular, renal, and hepatic domains. Importantly, these outcomes were generated with original rDNA semaglutide, including in trials that enrolled Asian and Indian populations.[13,18,19] Comparable outcome data are not yet available for synthetic-route semaglutide copies. This creates an important evidentiary gap: clinical benefits established for original rDNA semaglutide cannot be assumed to apply automatically to products manufactured through a different route solely on the basis of apparent molecular similarity.

Table 1. Original rDNA Semaglutide's Across the CKLM Spectrum with Clinical Benefits, Key Evidence, and Recent CDSCO Approvals in India

Domain	Semaglutide benefit	Key evidence	Recent approvals by DCGI/CDSCO-India	ADA Grade
C – Cardiovascular	14%–27% reduction in MACE outcomes	SOUL, SELECT, SUSTAIN-6 [6–8]	Oral original rDNA Semaglutide is now approved by CDSCO for “primary cardiovascular prevention” in T2D	Grade A
	31% reduction in cardiovascular death or worsening heart failure	SELECT heart-failure subgroup [32]		
K – Kidney	24% reduction in Major kidney-disease events	FLOW & REMODEL [9,27,33]	Original rDNA Semaglutide 1 mg, is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease with T2DM and CKD	Grade A

L – Liver	37% - Fibrosis improvement	ESSENCE [10]	Original rDNA Semaglutide 2.4 mg approved by CDSCO for MASH irrespective of BMI and diabetes status	Grade A
	63% MASH resolution	ESSENCE [10]		
M – Metabolic	Upto 18% Weight reduction Upto 2.8% HbA1C reduction 40% achieved ≥20% BMI reduction	PIONEER, SUSTAIN, STEP and SELECT STEP TEENS [4,5,17,34]	Original rDNA Semaglutide 2.4 mg approved by CDSCO for childhood obesity (aged ≥12 years)	Grade A

Abbreviations:

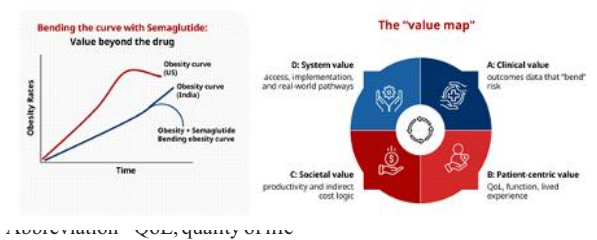
BMI, body mass index; CDSCO, Central Drugs Standard Control Organisation; CKD, chronic kidney disease; CV, cardiovascular; DCGI, Drugs Controller General (India); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, glycated haemoglobin; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; r-DNA, recombinant DNA; T2D, type 2 diabetes. Trial abbreviations: SOUL, oral-semaglutide cardiovascular-outcomes trial; SELECT, Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; STEP, Semaglutide Treatment Effect in People with Obesity; PIONEER, Peptide Innovation for Early Diabetes Treatment; FLOW, Evaluate Renal Function with Semaglutide Once Weekly; REMODEL, semaglutide renal mechanism-of-action study; ESSENCE, phase 3 semaglutide trial in MASH.

Bending the Obesity Curve with Semaglutide

Trials show efficacy under controlled conditions; population data show real-world impact at scale. The US offers the most mature such data, given its earlier GLP-1 uptake.[35] National survey data show adult obesity prevalence rose almost continuously from 25.5% in 2008 to a peak of 39.9% in 2022, then fell to about 37.0% in 2025 and 36.4% in the latest 2026 reading, the first sustained reversal in over a decade.[35,36] Separate examination-based surveillance recorded a fall from 42.4% (2017–2018) to 40.3% (2021–2023), also a first downturn in over a decade, though youth obesity kept rising over the same period. This decline lines up closely, in timing and by age group, with rising self-reported GLP-1 use for weight loss: from 5.8% of US adults in February 2024 to about 12.4% in late 2025 and around 15% in 2026.[35] The age groups with the largest obesity declines, 40–49 and 50–64, are also those with the highest GLP-1 use, shown. However, these are observational population-level data and do not establish causality; other demographic, behavioural, and public-health factors may also have contributed.[37] The findings are therefore best interpreted as an emerging association between wider GLP-1 use and a possible shift in the long-standing US obesity trajectory. During much of this observation period, use was predominantly represented by originator GLP-1 products, providing an early real-world context for considering their potential population-level impact.

The value of semaglutide extends beyond weight reduction alone. By altering the long-term trajectory of obesity, semaglutide has the potential to reduce downstream clinical risk while also improving quality of life, physical function, and overall patient experience. These benefits may translate into broader societal gains through improved productivity and lower indirect costs, while also creating health-system value through more effective care pathways, implementation, and access. Viewed together, these dimensions support a broader assessment of semaglutide that incorporates clinical, patient, societal, and system-level outcomes rather than focusing only on kilograms lost.

Figure 3. Beyond the Drug: Clinical, Patient, Societal, and Health-System Value[38]



Manufacturing Science: Why Original rDNA Semaglutide's Manufacturing Route Sets the Reference Standard

India's national drug regulator has approved original rDNA semaglutide separately for its two main indications, type 2 diabetes and, later, chronic weight management.[13] Following the March 2026 patent expiry, domestic manufacturers launched synthetic-route generic formulations within weeks, at a lesser price .[3] This section sets out why that price difference is not the only one that matters.

Manufacturing route and product characteristics

Original rDNA semaglutide is produced through recombinant expression of the peptide backbone in *Saccharomyces cerevisiae*. In contrast, many follow-on products are manufactured predominantly by solid-phase peptide synthesis.[13,39] Because these processes differ fundamentally, they may also generate different process-related and peptide-related impurities. Recombinant manufacture is associated mainly with fermentation- and host-cell-derived impurities, whereas chemical synthesis may introduce sequence variants, racemisation, incomplete coupling products, and residual metals .[13,40] These characteristics may influence stability, aggregation, and immunogenic potential. Therefore, confirmation of the same primary peptide sequence is only one component of comparability. Assessment of purity, impurity pattern, structural integrity, stability, and immunogenicity remains necessary before clinical equivalence can be assumed.[41,42] The low immunogenicity observed in the original rDNA semaglutide clinical programme applies specifically to that validated manufacturing process and product.

Regulatory frameworks treat approval and interchangeability as separate questions

The regulatory treatment of synthetic semaglutide is not uniform across jurisdictions. In India, CDSCO specifically states that a synthetically manufactured drug referring to a previously approved rDNA-derived product should be submitted as a subsequent new drug, with safety and efficacy considered under the New Drugs and Clinical Trials Rules, 2019.[43] The European framework takes a comparability-based approach. For a synthetic peptide developed against a biologically manufactured reference medicine, the EMA requires differences in structure, biological activity, purity and impurity profiles to be characterised and justified. Although such products do not qualify for the biosimilar pathway, the scientific principles used to establish high similarity remain relevant.[44] The US approach has evolved further. In July 2026, the FDA issued revised product-specific guidance for generic Semaglutide, explicitly supporting development through the ANDA framework, while placing product-specific requirements on demonstrating equivalence.[45] Thus, the key regulatory issue is not manufacturing route alone, but whether the evidence generated for a particular product is sufficient to meet the standards of the applicable regulatory pathway. Table 4 summarises how the three regulators differ in authority structure and classification approach, even while converging on this same principle.[13]

Table 2. Regulatory Frameworks for Peptide Follow-On Products: United States, European Union, and India[3,13]

Regulatory aspect	US FDA	EMA	India (CDSCO)
Regulatory authority	US FDA, mainly through CDER	EMA via CHMP and national competent authorities	CDSCO under the Drugs Controller General of India
Governing legislation	FD&C Act; PHS Act (limited cases)	Regulation (EU) No. 2019/6, Regulation (EC) No. 726/2004, Directive 2001/83/EC	Drugs and Cosmetics Act, 1940; New Drugs and Clinical Trials Rules, 2019

Product classification	Molecule-centric and risk-based; chemically synthesised peptides <40 amino acids usually regarded as small molecules	Molecule-centric	Process-centric and conservative; peptides often regulated under biologics-like frameworks regardless of size
Follow-on/generic pathway	Streamlined ANDA based on pharmaceutical equivalence and bioequivalence, where sufficient	Article 10(4) for biosimilars; Article 10(1) for generics	No clearly established abbreviated pathway; often evaluated similarly to a new drug or biosimilar

Product-level comparison: original rDNA semaglutide versus synthetic semaglutide

Table 3 sets side by side what is currently documented for the two manufacturing routes at the product level: evidence base, regulatory footprint, device, and approved indications. The asymmetry is stark, and it reflects the current state of published, product-specific evidence rather than some inherent property of synthetic peptides in general. The gap could in principle narrow as more comparative data accumulate.

Table 3. Original (rDNA) Semaglutide Versus Synthetic Semaglutide: Product-Level Comparison [3,13]

Parameter	Original rDNA semaglutide	Synthetic semaglutide
Manufacturing technology	Recombinant DNA (rDNA) fermentation with synthetic side-chain modification	Total chemical synthesis (solid-phase peptide synthesis)
Clinical use since	2017	From March 2026 (India)
Safety and efficacy evidence base	50+ clinical trials; 60,000+ trial participants	Phase 3 non-inferiority data in limited indications, in India only, to date
Regulatory approval footprint	India and 75+ countries	India
Patient experience	>49 million patient-years of exposure	Under 6 months of marketed use
Approved indication — diabetes	Adjunct to diet and exercise for glycaemic control in type 2 diabetes	Approved in type 2 diabetes
Approved indication — obesity	Adjunct to reduced-calorie diet and physical activity for chronic weight management	Approved in chronic weight management
Cardiovascular indication	Approved to reduce MACE risk in adults with type 2 diabetes and established CVD, and in adults with established CVD and overweight/obesity. Also approved in India as oral semaglutide for primary cardiovascular prevention in type 2 diabetes.	No cardiovascular outcomes trial data; no cardiovascular label indication
Renal indication	Approved to reduce risk of sustained eGFR decline, kidney failure, and cardiovascular death in type 2 diabetes with CKD	No data; no renal label indication
MASH indication	Approved indication for non-cirrhotic MASH with F2–F3 fibrosis	No data; no indication

Adolescent indication	Approved in adolescents aged 12+ with obesity as an adjunct to lifestyle intervention	No data; no indication
Device	Standardised prefilled pen, no push-button extension required	Push-button pen or non-standard presentations reported

Synthesised from Mohan et al. (2026) and Teli et al. (2026), drawing on manufacturer and regulator-submitted comparative material. Formulation strengths are described generically here (diabetes-indicated: 0.25/0.5/1 mg; weight-management-indicated: 0.25/0.5/1.0/1.7/2.4 mg); brand names are listed in the Acknowledgements. This is a product-comparability summary, not a claim that any named Indian manufacturer's specific formulation has failed a quality assessment.

Mohan et al. (2026) proposed ABCDE, an author-developed checklist rather than a regulator-endorsed standard, for judging whether a semaglutide product is genuinely comparable to the reference original rDNA semaglutide.[3] Approval doesn't guarantee interchangeability. Bioequivalence within the standard 80–125% exposure range bounds pharmacokinetic difference, not clinical outcome. Consistency of manufacture can vary even when the intended sequence is identical. Device performance affects real-world dosing accuracy, and the FDA has documented five- to twenty-fold overdoses linked to non-standard presentations. And evidence, in the end, is what separates a product that resembles semaglutide from one that has actually been shown to work like it. A product should be treated as comparable only once it clears all five bars, not the first one alone.

Indian Comparative Trials: What Has and What Has Not, Been Tested for Synthetic Copies

Some head-to-head data for Indian-manufactured semaglutide formulations now exist, and deserve accurate citation rather than being overlooked. Sharma et al. report a phase III randomised non-inferiority trial comparing a synthetically manufactured semaglutide injection against reference semaglutide for chronic weight management in Indian adults with obesity, meeting its pre-specified non-inferiority margin on weight-loss endpoints.[46] The study by Kapoor et al. similarly compared once-weekly semaglutide formulations in Indian adults with obesity in a phase III, randomised, active-controlled, non-inferiority design.[47]

These are a genuine and welcome start, but narrower in scope than the evidence. Both trials were built around obesity and weight-management endpoints over a relatively short follow-up and relatively smaller sample sizes; neither was designed or powered to assess cardiovascular, renal, or hepatic outcomes, nor long-term immunogenicity or aggregation-related safety of the kind discussed. Demonstrating non-inferiority on weight loss is a meaningful and necessary step, but it answers a narrower question than the one SELECT, FLOW, and ESSENCE were designed to answer for original rDNA semaglutide. Extrapolating cardio-renal-hepatic protection from a weight-loss non-inferiority trial is not methodologically supportable, a point consistent with how regulators treat follow-on peptide evidence more broadly. [3,13]

The Public Health Value Argument: Evidence Over Price

Original rDNA semaglutide's public health value is not fully captured by its price, and price alone is not a sufficient basis for treating it as interchangeable with synthetic copies. The breadth of demonstrated benefit is currently unique to original rDNA semaglutide. No synthetic copy of semaglutide has matching trial evidence across CKLM domains, and a health system that values prevented cardiovascular events, preserved kidney function, resolved steatohepatitis, and reduced disability from osteoarthritis is, in effect, valuing a body of evidence that presently exists for one manufacturing route only. The Indian non-inferiority trials in close the weight-loss question, not the cardiovascular, renal, hepatic, or long-term immunogenicity questions that account for most of original rDNA semaglutide's demonstrated public health value. Until synthetic copies generate their own dedicated outcomes evidence, treating them as automatically equivalent substitutes overstates what has actually been shown.

None of this argues against generic competition, which has a legitimate role in expanding access, nor does it claim synthetic semaglutide is

unsafe. The claim is narrower: that the choice between original and synthetic semaglutide in India should rest on what each product's evidence base actually contains, using a framework such as ABCDE, rather than on price as the only relevant variable. Where the clinical stakes are highest, in chronic, preventive, multi-organ therapy for a population with India's disease burden, the gap between "approved" and "proven equivalent" is exactly where public health value is won or lost.

Seen this way, public health value is also a total cost-of-care question, not only an acquisition-price one. Reductions in cardiovascular events, delayed progression toward dialysis-dependent kidney disease, and lower morbidity from obesity and MASH each carry downstream hospitalisation and productivity costs that an evidence-based choice between original and synthetic semaglutide can influence. For public payers in India, this argues for pragmatic clinical pathways, clear referral criteria between endocrinology, cardiology, nephrology, and hepatology, and monitoring frameworks that weigh long-term value alongside the lower acquisition price of synthetic copies, rather than acquisition price in isolation.

Safety, Tolerability, and Real-World Considerations

The safety profile of original rDNA semaglutide is well established across its STEP weight-management and SUSTAIN glycaemic clinical development programmes. Adverse events were predominantly gastrointestinal in nature and generally mild-to-moderate in severity and transient. In STEP 1, discontinuation due to gastrointestinal adverse events occurred in 4.5% of participants receiving semaglutide versus 0.8% with placebo, with overall study-drug discontinuation of 7.0% versus 3.1%; in SUSTAIN-6, discontinuation due to adverse events occurred in 11.5% (0.5 mg) and 14.5% (1.0 mg) of participants receiving semaglutide versus 8.0% with pooled placebo.[4,8] In both programmes, the large majority of participants completed their assigned treatment. These safety data relate specifically to original rDNA semaglutide and cannot be directly extrapolated to synthetic-route formulations with different manufacturing and impurity profiles. A similar, largely gastrointestinal, tolerability profile has also been reported for original rDNA semaglutide in the FLOW renal-outcomes population, indicating a consistent safety signal across the CKLM continuum.[9] In routine practice, safety also depends on dosing accuracy, device design, storage conditions, and product authenticity. The FDA has reported clinically significant dosing errors with compounded multidose semaglutide preparations, including substantial overdoses.[48] In India, rapid market expansion following patent expiry, together with the global increase in counterfeit GLP-1 products, highlights the importance of stringent quality control, pharmacovigilance, appropriate cold-chain management, and supervised prescribing.[13,49]

Knowledge Gaps and Future Research Directions

Five gaps stand out as named research priorities, set out in Table 4

Table 4. Key Knowledge Gaps and Research Priorities Identified in This Review

Domain	Specific gap	Suggested next step
Manufacturing/quality equivalence	No published, product-specific comparative impurity, stability, or immunogenicity analysis of individual marketed Indian generic semaglutide formulations against the rDNA-derived reference standard was identified	Independent, regulator-commissioned analytical comparison (peptide mapping, impurity profiling, in silico/in vitro immunogenicity risk assessment) across each marketed formulation
Hard-outcomes evidence for synthetic copies	Existing Indian comparative trials (Sharma et al., 2026; Kapoor et al., 2026) test weight-loss non-inferiority only[46,47]	Dedicatedcardiovascular , renal, and hepatic outcomes trials for synthetic-route semaglutide, mirroring theSELECT/FLOW/ESSENCE design
Long-term immunogenicity surveillance	Anti-drug antibody and aggregation data exist for original rDNA semaglutide (Staby et al., 2020) but not for marketed Indian synthetic copies[41]	Prospective, multi-year immunogenicity registry spanning all marketed Indian formulations

CKLM staging validation in Indian populations	AHA/ACC/ADA/ASN staging thresholds were derived largely from Western cohorts	Validation study of CKM/CKLM staging thresholds against Indian and South Asian body-composition and risk data
Real-world pharmacovigilance post-generic-entry	Generic entry is too recent (March 2026) for real-world outcomes or adverse-event data to exist yet	Prospective pharmacy-claims or dispensing-registry study tracking adverse events and effectiveness by manufacturing route

CONCLUSION

This review set out to reframe the semaglutide conversation in India around demonstrated value rather than price alone. The clinical case for original rDNA semaglutide is broad and specific: durable weight loss, a 20% reduction in major cardiovascular events, a 24% reduction in major kidney events, resolution of steatohepatitis in a majority of treated patients, and additional benefit in heart failure, peripheral artery disease, osteoarthritis, and possibly cognitive decline, built on more than 49 million patient-years of exposure. India's generic transition has solved the price problem quickly. It has not yet closed the evidence gap. Recombinant and synthetic manufacturing routes are not interchangeable by default, and the regulatory literature in India, the US, and the EU treats this as an open, product-specific question rather than a formality. Early Indian non-inferiority trials are a genuine start but address weight loss alone, not the cardio-renal-hepatic outcomes that account for most of original rDNA semaglutide's demonstrated public health value. Until synthetic copies build a comparable evidence base of their own, the public health value already demonstrated for original rDNA semaglutide, across CKLM systems, in Asian and Indian populations specifically, and at a scale of tens of millions of patient-years, is reason enough to weigh evidence, not price, as the primary basis for clinical and policy choices about semaglutide in India. More broadly, cardiovascular, kidney, liver, and metabolic disease should be treated as a single, convergent non-communicable disease priority for India, one that calls for coordinated management across endocrinology, cardiology, nephrology, and hepatology rather than siloed, single-organ care, with endocrinologists well placed to identify high-risk patients early and to anchor therapy choice to organ-protection evidence rather than HbA1c control alone.

Acknowledgements:

This review refers to medicines by international nonproprietary name (INN) semaglutide, and does not name specific companies or brand products in the text, to keep the argument focused on the molecule and the evidence it has generated. For transparency, the principal brand and manufacturer names behind the source material are listed here instead of in the body text: Original brand names for semaglutide: Ozempic (diabetes-indicated formulation, 0.25/0.5/1 mg) and Wegovy (weight-management-indicated formulation, 0.25/0.5/1.0/1.7/2.4 mg), with Rybelsus as the oral formulation; original rDNA semaglutide manufacturer: Novo Nordisk A/S.

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