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LETTER TO THE EDITOR

Short-Term HbA1c Non-Inferiority of Synthetic Semaglutide Should Not Be Conflated With Full Therapeutic Interchangeability

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To the Editor,

We read with interest the study by Gopalakrishnan et al. [1] comparing a synthetic semaglutide injection with reference innovator semaglutide in Indian adults with type 2 diabetes (T2D) who were inadequately controlled on metformin. The study is timely and clinically important because affordable semaglutide formulations may improve access to GLP-1 receptor agonist (GLP-1RA) therapy in India. This issue is also aligned with a recent discussion by Wen et al. [2], which reviewed the emerging GLP-1RA biosimilar landscape, highlighting liraglutide and semaglutide as leading candidates for biosimilar development and emphasizing affordability, access and the need for comparative evidence. More recently, Hussain et al. [3] reported prospective real-world evidence from Pakistan showing clinically meaningful reductions in HbA1c and weight with biosynthetic semaglutide in routine care, while also acknowledging the limitations of a single-arm, non-comparator observational design. Against this evolving evidence base, precision in distinguishing short-term clinical non-inferiority, real-world effectiveness, regulatory comparability and full therapeutic interchangeability becomes especially important.

Gopalakrishnan et al. [1] conducted a multicenter, randomized, open-label, active-comparator, 24-week study that applied an identical titration algorithm in both arms and met the prespecified HbA1c non-inferiority endpoint. The broadly comparable findings in body weight and short-term safety, including immunogenicity data, are also reassuring. However, implying 'full therapeutic interchangeability' requires clarification. A 24-week HbA1c non-inferiority trial can demonstrate short-term glycemic comparability under the studied titration algorithm, but it cannot, by itself, establish therapeutic interchangeability across doses, switching contexts and clinical indications. The manuscript refers to side-by-side analytical testing, orthogonal physicochemical assessment, in vitro bioassays and bioequivalence studies, and links these data to full therapeutic interchangeability. Yet the authors did not cite full peer-reviewed reports on underlying analytical comparability, impurity profiles, in vitro potency, device performance, stability, or in-use stability data, beyond an abstract on pharmacokinetic bioequivalence. The short-term HbA1c non-inferiority does not directly prove full interchangeability across all semaglutide indications and populations. This distinction is important because semaglutide is no longer only a glucose-lowering drug; its cardiovascular (CV) and kidney outcomes claims carry major clinical consequences in people with atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease (CKD).

Several study design and reporting features temper interpretation: First, the trial used HbA1c-guided adaptive dose escalation rather than fixed-dose comparison. Dose escalation decisions began at Week 8, after only 4 weeks of 0.5 mg exposure, and were subsequently repeated monthly, only if HbA1c $\geq$ 7.5%. Since HbA1c is a lagging glycemic biomarker, these interim HbA1c values may reflect cumulative prior exposure rather than the steady-state pharmacodynamic effect of the current dose. Thus, the design supports short-term glycemic comparability under a shared titration algorithm, but does not establish dose-level equivalence at 0.5, 1.0 or 2.0 mg. Second, the primary efficacy analysis was performed in the per-protocol (PP) population,

with an intention-to-treat (ITT) analysis reported as supportive. A clearly presented modified ITT (mITT) analysis in the main report would have strengthened robustness assessment. Third, the handling of rescue-medication eligibility warrants clarification: three patients reportedly met protocol-defined rescue criteria but did not receive rescue therapy. The impact of these protocol deviations on the PP and ITT estimates should have been reported. Fourth, the table reports duration as the median and interquartile range (IQR), which is appropriate for a skewed variable, but the limitations section states that 'mean duration' is short. Reporting both the mean ± SD and the median (IQR) would help readers assess the distribution and generalizability. This is relevant because a short duration of T2D among metformin-treated patients limits generalizability in patients with long-standing T2D, insulin use, multiple background therapies, or CKD or ASCVD. Fifth, immunogenicity reporting should be interpreted as short-term screening rather than definitive immunologic equivalence. The absence of anti-drug antibody (ADA) and neutralizing antibody (NAb) is reassuring, but the exposed sample sizes of approximately 150–190 participants per test arm are too small to rule out uncommon ADA/NAb responses. If NAb testing was reflexive because ADA was negative, the manuscript should state this explicitly: 'No confirmed ADA was detected; therefore, NAb testing was not triggered'. That is more precise than implying universal NAb testing. Moreover, just a two-point-in-time testing, such as pre-dose and post-24-week dosing, is not sufficient evidence of the absence of immunogenicity. Ideal ADA/NAb reporting would include ADA-evaluable denominators, assay sensitivity, cut-off points, treatment-induced versus treatment-boosted ADA, transient versus persistent ADA, serial or quantitative ADA titers, NAb testing strategy and clinical correlation.

Finally, the authors appropriately acknowledge that the study was not designed to evaluate CV or renal outcomes. However, the subsequent statement that similar benefits 'may be anticipated' on the basis of bioequivalence and clinical comparability requires careful qualification. Any clinical interpretation should remain aligned with the approved local label. More importantly, any expectation of similar CV or renal benefit should be understood as regulatory and pharmacological extrapolation from the totality of evidence, not as an outcome demonstrated by this 24-week HbA1c non-inferiority trial.

In summary, Gopalakrishnan et al.'s study provides useful and reassuring evidence of short-term glycemic non-inferiority and comparable short-term tolerability of synthetic semaglutide versus reference semaglutide in the Indian T2D population studied. However, the phrase 'full therapeutic interchangeability' risks overextending the available clinical evidence. A more proportionate conclusion would be that the test product demonstrated short-term HbA1c non-inferiority under the trial conditions. We support the development of high-quality generic semaglutide and recognize the importance of improved access. Nevertheless, we need to distinguish between regulatory approval based on a totality-of-evidence dossier, a short-term clinical non-inferiority demonstrated through a modest-sized 24-week Phase 3 trial and an extrapolated expectation of CV and kidney outcome benefit. Conflating these concepts may set an unfortunate precedent for future generic peptides.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Peer Review

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