ISSN: 2755-1059

Journal of Nephrology & Endocrinology Research

SCIENTIFIC Research and Community

Research Article

Open Access

Renal Effects of Liraglutide Biosimilar Versus Reference Liraglutide in Indian Patients with Type 2 Diabetes: Post Hoc Findings from a Phase III Trial

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ABSTRACT

Background: Chronic kidney disease is a common complication of type 2 diabetes mellitus (T2DM) and contributes substantially to cardiovascular morbidity and mortality. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), including liraglutide, have demonstrated potential renal benefits in cardiovascular outcomes trials. Data on renal parameters with liraglutide biosimilars, particularly in Indian populations, remain limited.

Methods: This post hoc exploratory analysis evaluated renal parameters from a randomized Phase III trial comparing a liraglutide biosimilar with reference liraglutide in Indian patients with T2DM. Changes in estimated glomerular filtration rate (eGFR), serum creatinine, and blood pressure were assessed from baseline to week 24. Within-group and between-group comparisons were performed using unadjusted statistical analyses.

Results: A total of 241 participants with complete renal data were included (liraglutide biosimilar, n=123; reference liraglutide, n=118). Both treatment groups demonstrated statistically significant within-group improvements in eGFR and reductions in serum creatinine over 24 weeks. No statistically significant differences were observed between the biosimilar and reference liraglutide groups for eGFR or serum creatinine at week 24. Modest reductions in systolic and diastolic blood pressure were observed in both groups.

Conclusion: In this post hoc analysis, liraglutide biosimilar and reference liraglutide were associated with comparable short-term changes in eGFR and serum creatinine in patients with T2DM. Given the exploratory design, short duration of follow-up, and reliance on surrogate renal markers, these findings should be interpreted cautiously. Prospective studies with longer follow-up and comprehensive renal endpoints are required to further characterize renal outcomes with liraglutide biosimilars.

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Received: November 04, 2026; **Accepted:** November 09, 2026; **Published:** November 19, 2026

Keywords: Liraglutide Biosimilar, Reference Liraglutide, eGFR, Serum Creatinine, Blood Pressure, Chronic Kidney Disease

Introduction

Chronic Kidney Disease (CKD) is a common and serious complication of Type 2 Diabetes Mellitus (T2DM) and is associated with increased cardiovascular morbidity and mortality [1]. Approximately 40% of individuals with T2DM develop some degree of CKD, making diabetic kidney disease a leading cause of end-stage renal disease worldwide [2,3]. CKD in patients with T2DM has become widely acknowledged as a major health issue, such that Dialysis-dependent chronic kidney disease is mostly caused by diabetic kidney disease [4]. The presence of CKD in Patients with T2DM increases the susceptibility to having a heart attack or stroke 3 times as compared to patients who have T2DM alone. START India study has shown the prevalence of CKD (eGFR < 60 ml/min/1.73 m2) in Patients with T2DM to be as high as 48% [5]. The pathogenesis of CKD in patients with T2DM involves many contributors beyond hyperglycaemia, such as hypertension, obesity, insulin resistance, and glomerular atherosclerosis, which exert kidney damage through metabolic, fibrotic, inflammatory, and hemodynamic mechanisms [6]. With this, the management of CKD and maintenance of renal function in Patients with T2DM becomes challenging and has gained attention more than ever before.

Optimal glycaemic management lowers the risk of developing early diabetic nephropathy [7,8]. Some glucose-lowering agents (e.g., Sodium Glucose Co-Transport 2 inhibitors – SGLT2i) appear to have glucose-independent effects on diabetic nephropathy and its progression. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) offer an effective treatment for Patients with T2DM and have beneficial effects on glycaemic control and weight loss [9]. The recent American Diabetes Association (ADA) 2024 guidelines recommend GLP-1RAs with proven cardiovascular (CV) benefit in individuals with T2DM with established atherosclerotic cardiovascular disease (ASCVD) or CKD [10]. as the secondary renal outcomes in landmark CV outcomes trials of GLP-1RAs have demonstrated their beneficial effects in reducing the onset and progression of macroalbuminuria and reducing eGFR decline,

indicating their reno-protective role in Patients with T2DM with CKD [11,12].

Short duration studies with GLP-1RAs like Liraglutide improve glycaemic control, reduce urinary albumin excretion, and increase urinary sodium excretion in Patients with T2DM [13,14]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome (LEADER) trial showed lower risks of cardiovascular outcomes, all-cause mortality, and microvascular outcomes with liraglutide than with placebo [15]. In this trial, the lower risk of microvascular outcomes was driven primarily by renal outcomes. Research indicates that the protective impact of GLP1-RAs on the kidneys is largely mediated by factors other than glycaemic control alone [16]. In the LEADER trial, HbA1c decrease accounted for only 25% of the kidney-protective benefits of these treatments [15]. Blood pressure reduction, body weight improvement, and albuminuria reduction are different pathways by which GLP-1RAs, such as Liraglutide, can prevent the progression of renal diseases and offer reno-protective benefits in Patients with T2DM over the long term [17,18]. Recently, a biosimilar formulation of liraglutide received marketing authorization in India after demonstrating glycemic efficacy and safety in a Phase III randomized clinical trial [19]. Considering the importance of renal outcomes in patients with T2DM and the paucity of evidence regarding the renal effects of liraglutide biosimilars, we performed a post hoc exploratory analysis of the Phase III trial. The analysis assessed changes in estimated glomerular filtration rate (eGFR), serum creatinine, and blood pressure over a 24-week treatment period, comparing the liraglutide biosimilar with the reference product in Indian patients with T2DM.

Materials and Methods

Study Design

The Phase III clinical trial design of Liraglutide biosimilar, the specific methodologies employed, and the key outcomes have been previously published [19]. This randomized, open label, parallel group, two-arm study with assessor blinding involved 17 clinical trial sites across India to assess the efficacy, safety and tolerability of liraglutide Biosimilar marketed by Glenmark Pharmaceuticals limited and developed by Levim Biotech LLP versus reference liraglutide in the treatment of Patients with T2DM already receiving treatment with other oral hypoglycaemic agents at stable dose (CTRI/ 2022/02/040261, 14/02/2022). Patients with type 2 diabetes who were between the ages of 18 and 65 and had baseline HbA1c values between 7% and 10% made up the study population. In addition to standard-of-care medication, a total of 256 Patients with T2DM were randomly assigned in a 1:1 ratio to receive either reference liraglutide (1.2 mg/day or up-titrated to the maximum dose of 1.8 mg/day) or liraglutide Biosimilar (1.2 mg/day). With the exception of the screening phase, the course of therapy lasted 24 weeks.

At the baseline visit, all patients recruited into the trial were started on either Biosimilar or Reference Liraglutide at a starting dose of 0.6 mg. Following at least 1 week of therapy, both treatment arms underwent dose titration to 0.6 mg until the maintenance dose was reached. The study was conducted in accordance with the Declaration of Helsinki, the New Drugs and Clinical Trial Rules, 2019 (CDSCO, India), and the consolidated guideline from the International Council for Harmonization (ICH). Since we decided to conduct a post hoc analysis of a published Phase III trial, no formal ethics committee approval was obtained for this study.

Parameters for Post Hoc Analysis and Study Endpoints

We planned to analyse the demographic and baseline clinical characteristics for all the included study participants. Since data on study participants included in the Phase III trial [(The clinical study protocol, informed consent forms, and all other study-related documents received approval from the relevant independent ethics committees and institutional review boards, as applicable.) The study was carried out in accordance with the approved protocol, the ethical principles outlined in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the ICH E6 (R2) Guideline for Good Clinical Practice (CPMP/ ICH/135/95), the New Drugs and Clinical Trial Rules, 2019 (CDSCO, India), and other applicable regulatory requirements. Patients who received the liraglutide biosimilar and were included in the present post hoc analysis had provided informed consent for participation in the parent Phase III study; therefore, no additional informed consent was required specifically for this post hoc analysis. The efficacy of Liraglutide Biosimilar compared with Reference Liraglutide was evaluated with respect to renal parameters, viz., estimated glomerular filtration rate (eGFR) and serum creatinine, from baseline to week 24. In addition to renal parameters, we evaluated changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Glycemic parameter (HbA1c) was previously evaluated in the Phase III trial Liraglutide Biosimilar versus Reference Liraglutide, and the results were published; hence, they were not included in our study.

Statistical Analysis

Raw data of the study participants were extracted and tabulated. We used SPSS software version 23 (San Diego, CA) for data analysis. Demographic characteristics of all the patients were captured, and a baseline comparison was done. For continuous variables, descriptive statistics were expressed as mean ± SD, while categorical variables were summarized using frequency counts. Post-normality assessment: within-group analysis was performed using a paired t-test, while intergroup comparison was performed using an independent samples t-test. A p-value of < 0.05 was statistically significant.

Therefore, Liraglutide Biosimilar can be a better-suited option for the management of Indian Patients with T2DM with renal impairment.

Results

Baseline Demographic and Clinical Characteristics

A total of 256 patients were included in the final analysis of the Liraglutide Biosimilar Phase III clinical trial. Out of those, 241 patients (n = 123 in the Liraglutide Biosimilar arm and n = 118 in the Reference Biologic arm) who had complete data on renal parameters till the end of the clinical trial (week 24) were included in the post-hoc analysis. The mean age of patients in the Liraglutide Biosimilar arm was 51.01 ± 7.95 years, while the mean age of patients in the Reference Biologic arm was 50.82 ± 7.51 years. Mean BMI of the patients in the Liraglutide Biosimilar study arm was 27.96 ± 4.82 Kg/m2, while in the Reference Biologic arm, the mean BMI was 28.12 ± 4.81 Kg/m2. Clinical characteristics, including glycemic and renal parameters, were recorded at baseline. The mean eGFR in the Liraglutide Biosimilar arm was 86.62 ± 21.99 ml/min/1.73m2 of body surface area (BSA), while in the Reference Biologic arm it was 87.58 ± 18.57 ml/min/1.73m2 of BSA. Likewise, the mean serum creatinine levels in the Liraglutide Biosimilar arm were 0.92 ± 0.22 mg/dl, while in the Reference Biologic arm were 0.92 ± 0.19 mg/dl. All the baseline clinical values were comparable between the

two study groups. All the demographic and clinical parameters of the included study participants were comparable between the two study groups and are depicted in Table 1.

Table 1: Demographic And Baseline Clinical Characteristics of the Study Participants

Demographic characteristics					
Parameter	**Treatment**	**N**	**Mean**	**Std. Deviation**	**p value**
	Liraglutide Biosimilar	123	51.01	7.95	0.852
	Reference Biologic	118	50.82	7.51	
	Liraglutide Biosimilar	123	161.79	7.78	0.114
	Reference Biologic	118	163.43	8.26	
	Liraglutide Biosimilar	123	72.98	12.10	0.205
	Reference Biologic	118	75.13	14.05	
	Liraglutide Biosimilar	123	27.96	4.82	0.797
	Reference Biologic	118	28.12	4.81	
	Liraglutide Biosimilar	123	81.30	7.13	.527
	Reference Biologic	118	81.90	7.51	
	Liraglutide Biosimilar	123	128.86	8.62	.933
	Reference Biologic	118	128.77	8.02	
	Liraglutide Biosimilar	123	86.62	21.99	.752
	Reference Biologic	118	87.58	18.57	
	Liraglutide Biosimilar	123	0.92	0.22	.593
	Reference Biologic	118	0.92	0.19	
	Liraglutide Biosimilar	123	8.34	0.76	.157
	Reference Biologic	118	8.59	0.79	
	Liraglutide Biosimilar	123	131.03	36.10	< 0.01
	Reference Biologic	118	147.31	41.33	
	Liraglutide Biosimilar	123	198.12	51.25	< 0.01
	Reference Biologic	118	223.02	63.29	

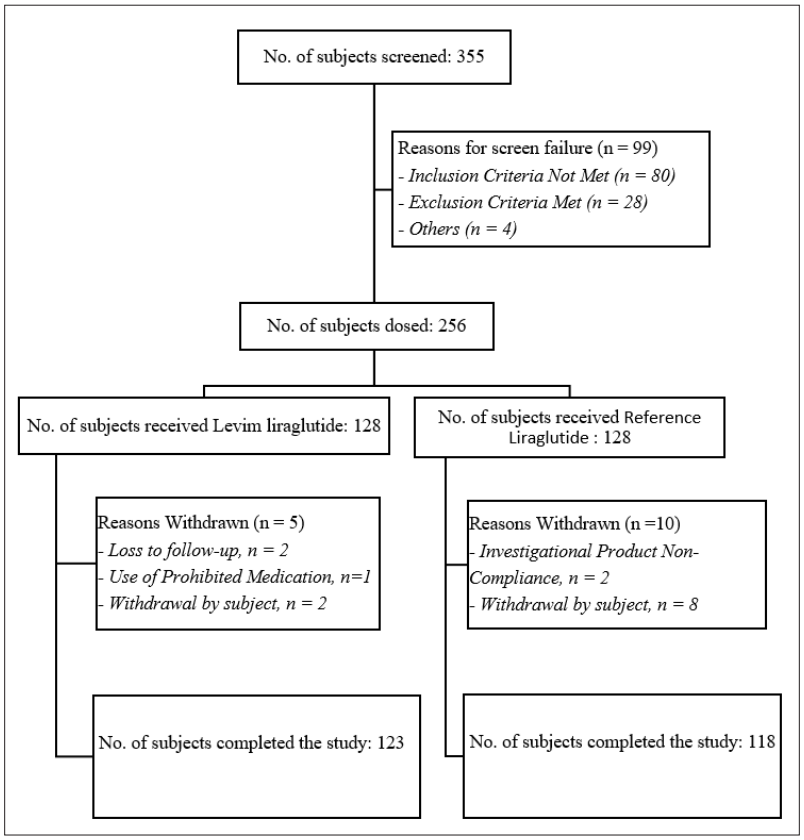


Figure 1: Subject Disposition

Table 2: Intra-Group Comparison in Renal Parameters in the Study Arms at Week 24

Inter group comparison in Renal parameters among the study arms at week 24					
Sr. no	**Parameter**	**Treatment**	**N**	**Week 24 (Mean ± SD)**	**p value**
1	eGFR	Liraglutide Biosimilar	123	91.50 ± 19.78	0.770
		Reference Biologic	118	92.21 ± 17.92	
2	Serum creatinine	Liraglutide Biosimilar	123	0.86 ± 0.20	0.848
		Reference Biologic	118	0.87 ± 0.18	

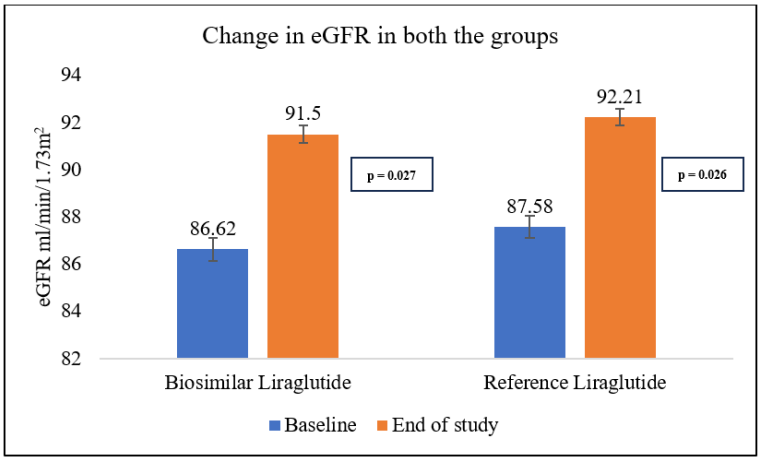


Figure 2: Change in eGFR from Baseline to Week 24

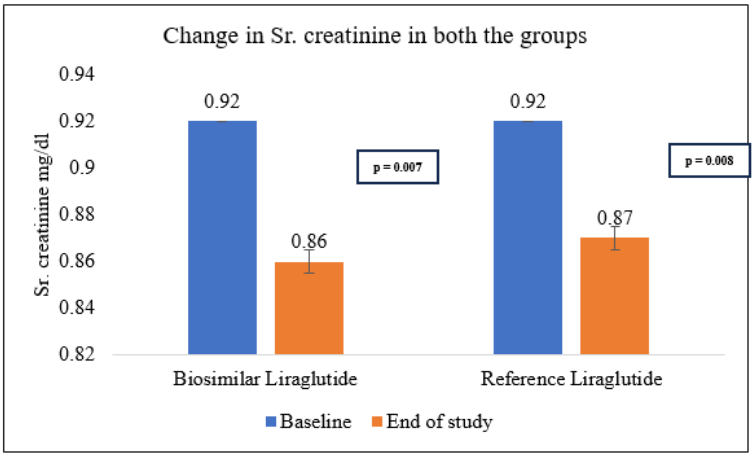


Figure 3: Change In Serum Creatinine from Baseline to Week 24

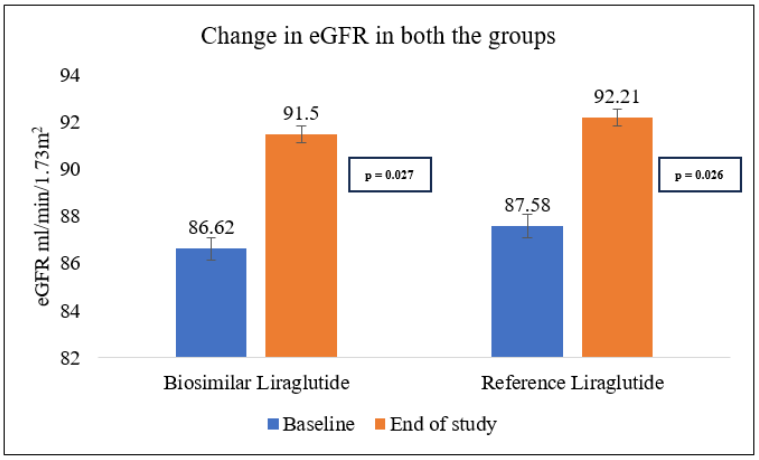


Figure 4: Change in SBP and DBP from Baseline to Week 24

Table 3: Intra Group Comparison in Blood Pressure in the Study Arms at Week 24

Inter group comparison in blood pressure among the study arms at week 24					
Sr. no	**Parameter**	**Treatment**	**N**	**Week 24 (Mean ± SD)**	**p value**
1	Systolic Blood pressure	Liraglutide Biosimilar	123	125.46	0.477
		Reference Biologic	118	126.16	
2	Diastolic Blood pressure	Liraglutide Biosimilar	123	79.46	0.023
		Reference Biologic	118	81.13	

Human Ethics and Consent to Participate Declarations:
Not applicable

Data Availability Statement:
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

Ethical Approval
The study was performed in accordance with the approved protocol and applicable ethical and regulatory standards, including the principles outlined in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the ICH E6 (R2) Guideline for Good Clinical Practice (CPMP/ICH/135/95), the New Drugs and Clinical Trial Rules, 2019 (CDSCO, India), and all other relevant regulatory requirements.

Trial Registration no: (CTRI.nic.in, no. CTRI/2022/02/040261). 04/02/2022

Acknowledgement & Funding
We acknowledge the contributions of the Glenmark Pharmaceuticals team members for their assistance with manuscript preparation and critical review. We also acknowledge Levim Biotech LLP and National Biopharma Mission (NBM), Biotechnology Industry Research Assistance Council (BIRAC), Department of Biotechnology (DBT), India, for their financial assistance towards the conduct of the Liraglutide Biosimilar Phase III clinical trial.

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