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Efficacy and safety of evogliptin versus sitagliptin as an add-on therapy in Indian patients with type 2 diabetes mellitus inadequately controlled with metformin: A 24-week randomized, double-blind, non-inferiority, EVOLUTION INDIA study

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ABSTRACT

Aim: This study aimed to assess efficacy and safety of evogliptin versus sitagliptin, when added to background metformin therapy in Indian patients with uncontrolled type 2 diabetes.

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Method: Overall, 184 patients with uncontrolled type 2 diabetes (7% ≤ HbA_{1c} < 10%) receiving ≥8 weeks of stable metformin monotherapy (≥1 g/day), were randomized to receive add-on treatment (evogliptin 5 mg or sitagliptin 100 mg) for 24 weeks. Primary endpoint was change in HbA_{1c} from baseline to 12 weeks (non-inferiority margin: <0.35).
Results: Mean reductions in HbA1c at 12 weeks in evogliptin- and sitagliptin-treated patients were −0.37 (1.06) and –0.32 (1.14), respectively. The adjusted mean difference between treatment groups was –0.022 (95% CI: –0.374, 0.330; P = 0.901), that demonstrated non-inferiority. Reductions in FPG and PPG were similar between evogliptin and sitagliptin at 12 and 24 weeks. Changes in body weight were comparable between the treatment groups. Patients achieving target HbA_{1c} < 7.0% (evogliptin, 26.7% vs. sitagliptin, 20%) was almost equal in both groups. Treatment-emergent adverse events occured in 52 patients (evogliptin, 25% and sitagliptin, 31.5%) and were generally mild.
Conclusions: Evogliptin was non-inferior to sitagliptin in HbA_{1c} reduction. It effectively improved glycemic control and was well tolerated in type 2 diabetes patients inadequately controlled by metformin alone.

1. Introduction

Diabetes is one of the leading global health issues of the 21st century. In 2017, ~73 million Indian adults had diabetes, and the number is estimated to increase by 85%, amounting to 134 million by 2045 making India the diabetes capital of the world [1]. In addition, the diabetes related disability adjusted life years (DALYs) rate has increased by 40% over the past two decades [2].

Most guidelines, recommend metformin for initial treatment of type 2 diabetes [3–6]. Since type 2 diabetes is a progressive and multifactorial condition, patients invariably require additional antihyperglycemic therapy. Dipeptidyl peptidase-4 (DPP-4) inhibitors are the recommended second-line or first-line therapy when metformin is contraindicated or not tolerated [3–5]. DPP-4 inhibitors enhance insulin secretion and reduce glucagon secretion by preventing inactivation of endogenous glucagon-like peptide-1 (GLP-1). DPP-4 inhibitors are associated with lower risk of hypoglycemia as the insulin-stimulating effect of DPP-4 inhibitors is glucose dependent and no inhibitory activity occurs at low glucose levels (<80 mg/dL) [7]. Moreover, evidence suggests that DPP-4 inhibitors exhibit neutral effects on cardiovascular outcomes [8–10]; thus, they are considered a valuable therapeutic option for type 2 diabetes.

Evogliptin, a novel potent and selective DPP-4 inhibitor, has demostrated glucose-lowering efficacy in both preclinical and clinical studies. In a Phase I trial, in comparison with placebo, evogliptin increased GLP-1 levels by up to 2.4-fold and reduced postprandial glucose (PPG) levels by 20%–35%; at steady state, after administration of once-daily dose for 10 days, DPP-4 inhibitory activity was sustained for over 24 h [11]. Recent studies have shown that first-line therapy with evogliptin 5 mg effectively improves glycemic control in patients with type 2 diabetes [12,13]. Park et al reported that a significantly greater proportion of patients receiving evogliptin achieved target HbA_{1c} levels (<6.5%) compared with those receiving placebo [13]. Moreover, Jaeseong et al have demonstrated that evogliptin does not require dose titration in renal impairment [14]. In a randomized, active-controlled trial conducted in Korean patients with uncontrolled type 2 diabetes on metformin, the efficacy of evogliptin was similar to that of sitagliptin [15]. In 2015, evogliptin received the first global approval in South Korea for use in type 2 diabetes patients inadequately controlled by diet and exercise as well as for those with uncontrolled type 2 diabetes on metformin monotherapy. Nevertheless, no studies have evaluated the effect of evogliptin in Indian patients with type 2 diabetes. Given the ethnic differences, efficacy and safety of evogliptin must be assessed in this population. Hence, in the present Phase III trial, we aimed to evaluate whether evogliptin is non-inferior to sitagliptin in terms of reduction in HbA_{1c} after 12 weeks of treatment in Indian patients with type 2 diabetes.

2. Subjects, materials and methods

This randomized, double-blind, double-dummy, active-controlled, parallel group, multicenter study was conducted at 18 centers across India between September 2017 and May 2018. The study was conducted in accordance with international and local Good Clinical Practice guidelines and approved by an independent ethics committee (Clinical trials registry – India [www.ctri.nic.in]: CTRI/2017/06/008891). All patients provided written informed consent to accept the fullest extent possible information about the study, in language and terms they were able to understand before participation. A copy of the signed and dated written informed consent was provided to the patient.

2.1. Patients

Patients with type 2 diabetes aged 18–65 years with inadequate glycemic control (7% ≤ HbA_{1c} < 10%) after receiving at least 8 weeks of stable metformin monotherapy (≥1 g/day), were enrolled in this study. Patients were excluded if they had type 1 diabetes, secondary or gestational diabetes; body mass index (BMI) > 40 kg/m^2; myocardial infarction or any major cardiovascular events within 6 months; chronic heart

failure (New York Heart Association Class III or IV); uncontrolled hypertension; diabetic ketoacidosis or hyperosmolar non-ketotic coma before screening; thyroid dysfunction; any malignancy (except treated basal cell carcinoma); pancreatitis or pancreatic cancer; gastrointestinal resection; or any abnormal laboratory finding.

2.2. Study design

Following a 1-week screening period, eligible patients were randomly assigned (1:1) to receive either evogliptin 5 mg once daily (or matching placebo) or sitagliptin 100 mg once daily (or matching placebo) for 24 weeks (Fig. 1a). Permuted block randomization method was used with block size of 4 to allocate treatment in 1:1 ratio. Patients were randomized using IWRS method with generation of central and competitive randomization schedule. The study included a 24-week double-blind and double dummy phase during which neither the investigator nor the patient knew which treatment received by the patient. Placebo tablets visually matched the active tablets in order to preserve the study blind. Double-blind study medications were given in individual bottles. Follow-up visits were planned at weeks 2, 4, 8, 12, 16, 20, and 24 of the treatment period. Body weight, vital signs (systolic and diastolic blood pressure and heart rate), physical examination, prior and current concomitant medications, compliance to study medications and adverse events (AEs) were recorded at all visits. Efficacy measures (fasting plasma glucose [FPG], PPG, and HbA_{1c}) and safety measures (urinalysis, hematology, and serum chemistry) were assessed at screening, randomization, week 12, and week 24. If FPG or HbA_{1c} remained above the threshold values (FPG > 270 mg/dL from week 0 to week 8, FPG > 240 mg/dL from week 8 to week 12, and FPG > 200 mg/dL or HbA_{1c} > 8.5% from week 12 to week 24), rescue medication, different from the on-going antidiabetic therapy class, was added at the investigator's discretion. These patients remained in the study until the last visit; however, data collected after initiation of rescue therapy were excluded from efficacy analysis but included in safety analysis. Patients continued metformin therapy (≥1 g/day) throughout the study. All patients who completed the 24-week treatment period and those who discontinued the study treatment, entered a 2-week safety follow-up phase wherein overall clinical outcomes and safety were assessed; during this period patients received treatment at the investigator's discretion.

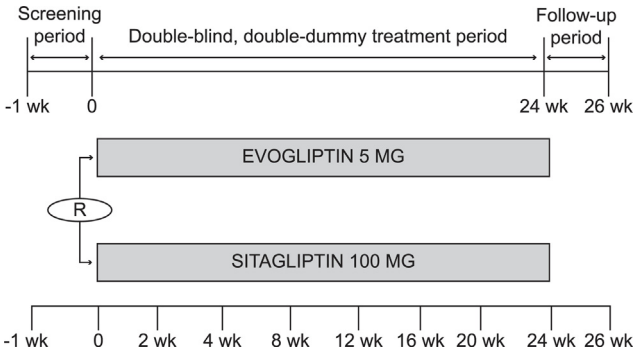


Fig. 1a – Study design.

2.3. Endpoints

The primary efficacy endpoint was change in HbA_{1c} from baseline to week 12. Secondary endpoints included changes in HbA_{1c} levels from baseline to week 24, proportion of patients achieving target HbA_{1c} of <7.0%; and changes in FPG, PPG and body weight from baseline to weeks 12 and 24. Safety endpoints included treatment-emergent adverse events (TEAEs; coded using the Medical dictionary for Regulatory Activities [MedDRA], version 21) and changes in clinical laboratory parameters, electrocardiogram and two- dimensional echocardiography findings from baseline to end of the study. All efficacy and safety laboratory parameters were analyzed in the central laboratory.

2.4. Statistical analysis

The study was designed to have an 80% power to establish non-inferiority (margin 0.35) of evogliptin 5 mg once daily vs. sitagliptin 100 mg once daily, with one-sided test at 95% confidence interval (CI). The standard deviation (SD) of change in HbA_{1c} from baseline until week 12 was assumed to be 0.85. Considering a 20% drop out rate, 184 patients were randomly assigned to either of the two treatment groups at a ratio of 1:1 (92 patients in each treatment arm).

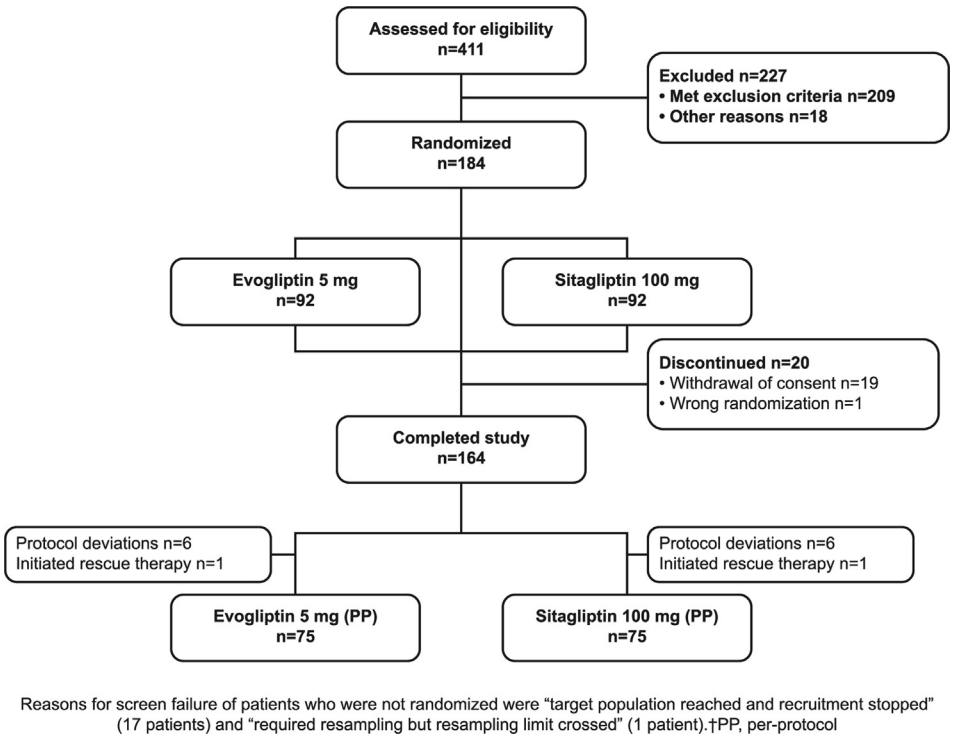
All baseline evaluations and safety analyses were performed for the intent to treat (ITT) population, defined as all randomized patients who received at least one dose of the study treatment. All primary and secondary efficacy endpoint(s) were analyzed based on the per-protocol (PP) population. Analysis of efficacy endpoints was performed using analysis of covariance (ANCOVA). The model included treatment arm and study centers as stratification factors and baseline HbA_{1c} as covariate. Categorical data were compared using chi-square test or Fisher's exact test. Continuous data were summarized using mean ± SD or median (minimum-maximum values of continuous variables). Discrete data were summarized using frequency counts (n) and percentages (%).

3. Results

3.1. Patient disposition and baseline characteristics

A total of 184 patients were randomized (evogliptin 5 mg, N = 92; sitagliptin 100 mg, N = 92) who received at least one dose of the study treatment (ITT population). Of 184 randomized patients, 20 patients (10 patients from each group) were discontinued and 164 patients completed the study (Fig. 1b).

Baseline demographics and clinical characteristics were similar between the two groups (Table 1). The mean age of participants was 50.3 (8.24) years (evogliptin, 49.3 [7.55] years; sitagliptin, 51.4 [8.79] years). Overall, a greater proportion of men participated in the study (52.7% men; 47.3% women). The mean duration of type 2 diabetes was 2.7 (3.42) years (median: 1.3 years; Q1, Q3: 0.5, 3.8 years). None of the patients



Reasons for screen failure of patients who were not randomized were "target population reached and recruitment stopped" (17 patients) and "required resampling but resampling limit crossed" (1 patient).†PP, per-protocol

Fig. 1b – Patients disposition.

Table 1 – Baseline demographics and clinical characteristics of study participants (intent-to-treat population).

	Evogliptin N = 92	Sitagliptin N = 92	Total N = 184
Age, years			
Mean (SD)	49.3 (7.55)	51.4 (8.79)	50.3 (8.24)
Median (Q1, Q3)	48.0 (43.5, 55.0)	53.0 (46.0, 57.5)	51.0 (45.0, 57.0)
Men, n (%)	49 (53.3)	48 (52.2)	97 (52.7)
Body weight, kg			
Mean (SD)	65.2 (11.86)	69.2 (13.14)	67.2 (12.64)
Median (Q1, Q3)	64.0 (57.1, 71.9)	67.5 (59.8, 77.7)	65.2 (58.4, 74.8)
BMI, kg/m^2			
Mean (SD)	25.1 (3.76)	27 (4.42)	26 (4.20)
Median (Q1, Q3)	24.8 (22.7, 27.0)	26.7 (23.6, 29.1)	25.8 (23.0, 28.1)
Duration of diabetes, years			
Mean (SD)	2.5 (3.15)	2.9 (3.67)	2.7 (3.42)
Median (Q1, Q3)	1.2 (0.5, 3.2)	1.6 (0.4, 3.8)	1.3 (0.5, 3.8)
HbA_{1c}, %			
Mean (SD)	8.28 (0.83)	8.28 (0.7)	8.28 (0.77)
Median (Q1, Q3)	8.1(7.65, 8.9)	8.15(7.7, 8.75)	8.1(7.7, 8.9)

Data are shown as mean (SD) or n (%); BMI: body mass index; HbA_{1c}: glycated hemoglobin.

were alcoholic or involved in drug abuse, and almost all enrolled patients (182 [98.9%]) were non-smokers.

3.2. *Efficacy*

Mean baseline HbA_{1c} level was 8.34 (0.75)% in the overall PP population and similar between both treatment groups (evogliptin, 8.33 [0.82]%; sitagliptin, 8.35 [0.67]%; $P = 0.905$). After 12 weeks of treatment, significant reductions in HbA_{1c} were observed in both groups (evogliptin, −0.37 [1.06]%; sitagliptin, –0.32 [1.14]%; $P < 0.05$ for both) (Table 2), and the results were comparable between the groups ($P = 0.783$). The adjusted mean difference (evogliptin vs. sitagliptin) in the change from baseline to week 12 was − 0.022% (95% CI: −0.374, 0.330; $P = 0.901$). Hence, after 12 weeks of treatment, evogliptin was non-inferior to sitagliptin in terms of reduction in HbA_{1c} level (upper limit of 95% one-sided CI was below the pre-specified limit [<0.35]). At 24 weeks, further reduction in

Table 2 – Change from baseline in HbA_{1c}, FPG, PPG, and patients achieving target control at week 12 and 24.

	Evogliptin N = 75	Sitagliptin N = 75	Adjusted mean difference between groups (95% CI)	p-value*
HbA_{1c}, %				
Week 12	−0.37 (1.06)	−0.32 (1.14)	−0.022 (−0.374, 0.330)	0.901
p-value#	0.0035	0.0177	–	–
Week 24	−0.55 (1.19)	−0.48 (1.21)	−0.043 (−0.401, 0.314)	0.810
p-value#	0.0001	0.0009	–	–
HbA_{1c} response rate (HbA_{1c} < 7%), n (%)				
Week 12	16 (21.3)	17 (22.7)	–	0.844
Week 24	20 (26.7)	15 (20.0)	–	0.334
FPG, mg/dL				
Week 12	−19.08 (71.23)	−24.74 (77.42)	−7.13 (−22.496, 8.237)	0.360
p-value#	0.0271	0.0084	–	–
Week 24	−22.96 (67.01)	−33.58 (79.73)	0.94 (−14.747, 16.629)	0.906
p-value#	0.004	0.0006	–	–
PPG, mg/dL				
Week 12	−21.45 (102.04)	−28.12 (82.63)	2.59 (−21.085, 26.274)	0.829
p-value#	0.0767	0.0046	–	–
Week 24	−25.4 (93.78)	−19.35 (78.53)	−7.45(−28.594, 13.684)	0.486
p-value#	0.0266	0.0415	–	–
Body weight, kg				
Week 12	−0.15 (1.46)	−0.23 (1.59)	0.015(−0.266:0.296)	0.915
p-value#	0.3750	0.2054	–	–
Week 24	−0.29 (2.27)	−0.36 (2.00)	0(−0.284:0.285)	0.999
p-value#	0.3056	0.1348	–	–

Data are shown as mean (SD) or n (%); FPG: fasting plasma glucose; PPG: postprandial glucose; HbA_{1c}: glycated hemoglobin.
* P values were derived from ANCOVA test for all parameters, except for HbA_{1c} response rate, which was derived from chisquare test.
# P values were derived using paired t-tests showing the difference versus baseline.

HbA_{1c} was observed in each treatment arm (evogliptin, −0.55 [1.19]%; sitagliptin, −0.48 [1.21]%; $P < 0.001$ for both groups); and the results were similar between the groups ($P = 0.713$). The adjusted mean difference (evogliptin vs. sitagliptin) in change from baseline to week 24 was −0.043% (95% CI: −0.401, 0.314, $P = 0.810$) (Table 2).

In order to assess the influence of baseline HbA_{1c} level on treatment effect, patients were categorized into two groups based on their baseline HbA_{1c} level (7%–8.5% and >8.5%–10%). Within each baseline HbA_{1c} subgroup, reductions in HbA_{1c} at week 12 and week 24 were comparable between the two treatment groups. The reductions in HbA_{1c} in evogliptin vs. sitagliptin groups at week 12 were −0.24 (0.89)% vs. −0.15 (0.95)% ($P = 0.631$) for baseline $HbA_{1c} < 8.5\%$; and −0.55 (1.26)% vs. −0.61 (1.38)% ($P = 0.861$) for baseline $HbA_{1c} > 8.5\%$. Similarly, reductions in HbA_{1c} for evogliptin vs. sitagliptin groups at week 24 were − 0.30 (0.99)% vs. −0.18 (0.98)% ($P = 0.549$) for $HbA_{1c} < 8.5\%$; and −0.96 (1.43)% vs. −1.03 (1.38)% ($P = 0.861$) for $HbA_{1c} > 8.5\%$.

After 12 and 24 weeks of treatment, a similar proportion of patients reached the HbA_{1c} target of <7.0% in each treatment group (evogliptin: 16/75 [21.3%] and 20/75 [26.7%], respectively; sitagliptin: 17/75 [22.7%] and 15/75 [20%], respectively) (Table 2).

The mean FPG level at baseline was numerically higher in the sitagliptin group (evogliptin, 162.13 [60.82] mg/dL vs. sitagliptin, 174.54 [63.41] mg/dL) (Table 2). However, reductions in FPG were similar between evogliptin and sitagliptin at 12 weeks (−19.08 [71.23] mg/dL vs. −24.74 [77.42] mg/dL; $P = 0.650$) and at 24 weeks (−22.96 [67.01] mg/dL vs. −33.58 [79.73] mg/dL; $P = 0.382$).

At baseline, mean PPG was 234.38 (83.68) mg/dL in the evogliptin group and 241.73 (85.23) mg/dL in the sitagliptin group. Reduction in PPG was comparable in both the groups after 12 weeks (−21.45 [102.04] vs. −28.12 [82.63] mg/dL; $P = 0.664$) and 24 weeks (−25.4 [93.78] vs. −19.35 [78.53] mg/dL, $P = 0.678$) of treatment.

No statistically significant changes were noted in body weight at weeks 12 and 24 in both treatment groups (Table 2). The use of rescue medication was minimal, with only 2 patients receiving them, each in evogliptin and sitagliptin group.

3.3. *Safety*

In total, 61 TEAEs were reported in 52 (28.3%) patients during the study (Table 3). Most TEAEs were mild (evogliptin, 27 events in 22 patients; sitagliptin, 33 events in 29 patients); 1 (1.1%) patient from the evogliptin group experienced urinary tract infection of moderate intensity. None of the TEAEs were serious AE. The study medication was neither interrupted nor discontinued and no patient withdrew from the study due to AEs.

Overall, 14 TEAEs were related to the study drug, of these, 10 TEAEs were probably related (evogliptin, 4 events in 4 [4.3%] patients; sitagliptin, 6 events in 5 [5.4%] patients) and 4 TEAEs were possibly related to the study drug (evogliptin, 1 event in 1 [1.1%] patient; sitagliptin, 3 events in 3 [3.3%]

Table 3 – Summary of treatment emergent adverse events.

	Evogliptin		Sitagliptin	
	No. of Events	Patients with events[†] n (%)95%CI	No. of Events	Patients with events n (%)95%CI
Total adverse events	28	23 (25) [16.55%:35.11%]	33	29 (31.5) [22.23%:42.04%]
AESI	4	4 (4.3) [1.20%:10.76%]	4	3 (3.3) [0.68%:9.23%]
Intensity of adverse events				
Mild	27	22 (23.9) [15.63%:33.94%]	33	29 (31.5) [22.23%:42.04%]
Moderate	1	1 (1.1) [0.03%:5.91%]	0	0 (0.0)
Severe	0	0 (0.0)	0	0 (0.0)
Relationship to study drug				
Probable	4	4 (4.3) [1.20%:10.76%]	6	5 (5.4) [1.79%:12.23%]
Possible	1	1 (1.1) [0.03%:5.91%]	3	3 (3.3) [0.68%:9.23%]
Unlikely	23	19 (20.7) [12.92%:30.36%]	24	21 (22.8) [14.72%:32.75%]
Events that continued till EOS	7	7 (7.6) [3.11%:15.05%]	10	10 (10.9) [5.34%:19.08%]
Hypoglycaemia	1	1 (1.1) [0.03%:5.91%]	1	1 (1.1) [0.03%:5.91%]

[†] One patient could have more than one event; AESI: adverse event of special interest, EOS: end of study.

patients). The most commonly reported AE was dyslipidaemia (evogliptin, 6 events in 6 [6.5%] patients; sitagliptin, 5 events in 5 [5.4%] patients). Most of these events were reported to be unrelated to the study drug and none of them resolved during the study. A total of 8 TEAEs of special interest (elevated amylase or lipase levels) were reported (evogliptin, 4 events in 4 [4.3%] patients; sitagliptin, 4 events in 3 [3.3%] patients). Of these events, only 2 events were found to be probably related to the drug (i.e. sitagliptin group). This rise in amylase and lipase levels was transient and less than 3 times the upper limit of normal laboratory range. Furthermore, these events resolved during the study. Majority of the TEAEs (44 events in 35 patients [19.0%]) were recovered (evogliptin, 21 events in 16 [17.4%] patients, sitagliptin: 23 events in 19 [20.7%] patients). Two hypoglycemia events were reported during the study; 1 event each in evogliptin and sitagliptin groups. Both events were mild and unlikely to be related to the study drug.

4. Discussion

Findings from this Phase III clinical trial demonstrated that evogliptin improved glycemic control similar to sitagliptin when given as an add-on treatment in Indian patients with type 2 diabetes not responding to optimal dose of metformin monotherapy. Evogliptin was found to be non-inferior to sitagliptin for reduction in HbA_{1c} at 12 weeks. Moreover, the proportion of patients achieving the HbA_{1c} target of <7% as well as reductions in FPG and PPG were similar between both groups at 12 and 24 weeks.

Results from the present study were comparable with those from a previous study which demonstrated similar efficacy of evogliptin and sitagliptin when used as second-line therapy in patients with type 2 diabetes [15]. Significant reductions in HbA_{1c} levels were observed in both evogliptin (−0.37 [1.06]%) and sitagliptin (−0.32 [1.14]%) groups after 12 weeks of treatment; in addition, HbA_{1c} levels were further reduced by − 0.55 (1.19)% and − 0.48 (1.21)%, respectively, at 24 weeks. Moreover, the magnitude of HbA_{1c} reduction observed in our study was consistent with those reported in previous studies on evogliptin [12,13,15] as well as other DPP-4 inhibitors [16–18]. Furthermore, in a meta-analysis of randomized controlled trials, compared with placebo, addition of DPP-4 inhibitors to metformin therapy resulted in HbA_{1c} reductions of −0.77% and −0.67% after 3 and 6 months, respectively ($P < 0.00001$ for both) [19]. Decrease in FPG, PPG and proportion of patients achieving target HbA_{1c} level of <7.0% observed in our study are similar to results from a previous study conducted by Hong et al. [15]. Moreover, higher but comparable reductions in HbA_{1c} were noted in evogliptin and sitagliptin treated patients with baseline HbA_{1c} of >8.5%−10%. In a previous study, evogliptin in combination with metformin improved HbA_{1c}, FPG and 7 point mean blood glucose levels over the long-term (up to 1 year) [15]. Taken together, the results of this study suggest that evogliptin is an effective antihyperglycemic therapy for uncontrolled type 2 diabetes.

DPP-4 inhibitors are typically considered as weight-neutral antidiabetics for type 2 diabetes, and our study corroborated this fact. Reduction in body weight from baseline to 12 weeks was −0.15 (1.46) kg and −0.23 (1.59) kg for evogliptin and sitagliptin, respectively, with no difference in the effect size between both treatment groups (adjusted mean difference: 0.015, 95% CI:−0.266, 0.296, $P = 0.915$). At 24 weeks, the reduction in body weight was −0.29 (2.27) kg and −0.36 (2.00) kg for evogliptin and sitagliptin, respectively (adjusted mean difference: 0.0, 95% CI: −0.284, 0.285, $P = 0.999$). These findings are concordant with findings from a meta-analysis which showed the effect size to be −0.6 kg (range, −0.1 to −1.6) of body weight reduction from baseline to 6 months after treatment [19].

Evogliptin treatment was well tolerated in our study with no severe AEs being reported during the study. TEAEs observed were mild, and similar to those reported in previous studies [12,13,15]. In addition, evogliptin had a neutral effect on body weight. Hypoglycemia events were rare and mild in severity. Hence, evogliptin had an acceptable safety profile and did not increase the risk of hypoglycemia.

4.1. *Limitations*

This study has certain limitations that the patient enrollment was restricted to patients with uncontrolled type 2 diabetes without any major comorbidities, therefore, real world clinical study with a large diversified patient population shall be required to be conducted in future to further evaluate the safety and efficacy.

5. Conclusion

In conclusion, this study demonstrated that evogliptin when added to background metformin therapy, was non-inferior to sitagliptin in lowering HbA_{1c} in Indian patients with uncontrolled type 2 diabetes. Evogliptin in combination with metformin was well tolerated and was not associated with any major safety concerns.

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Authors' Contributions

Design of Study: MKS, FJ, BA, RPA, RKP, RM, SB, SKG, AD, AS, AT, VS, and SS; Conduct and data collection: AKA, AA, BLNP, IB, JS, NM, KAVS, MS, MC, MKS, FJ, BAM, RPA, RKP, RM, SB, SKG, AD, AS, AT, VS, and SS; Statistical analysis and interpretation: AKA, AA, BLNP, IB, JS, NM, KAVS, MS, MC, AS, AT, VS, and SS; Drafting and revision of manuscript: AKA, AA, BLNP, IB, JS, NM, KAVS, MS, MC, MKS, FJ, BA, RPA, RKP, RM, SB, SKG, AD, AS, AT, VS and SS. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take the complete responsibility for accuracy of the data analysis and integrity of the data and work as a whole.

Declaration of Competing Interest

Ambrish Srivastava, Abhijit Trailokya, Vinayaka Shahavi, and Sachin Shende are the employees of Alkem Laboratories Limited, India. Authors declare no other competing interest.

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