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Efficacy and safety of teneligliptin versus vildagliptin as add-on to metformin or metformin and sulfonylureas in Indian patients with Type 2 diabetes mellitus

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ABSTRACT

Background: India is heading towards being the diabetes capital of the world. Prevention and control of diabetes-related complications can be achieved, with a target ofHbA1cless than 7.0%. Clinical studies have shown that gliptins in combination with metformin resulted in better glycemic control than high-dose metformin alone. Teneligliptin with a long plasma half-life isan attractive treatment option for patients failing on metformin or metformin plus sulphonylurea.

Objective: The primary objective of this study was to compare the reduction in fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2-h PPG), and HbA1c, in Vildagliptin group and the Teneligliptin group at 12, and 24 weeks with baseline values of two groups.

Methods: This was a 24-week, randomized, open-label study. Patients with type 2 diabetes, who were inadequately controlled on Metformin (500/850mg, twice a day) with/without Glimepiride (2/3mg, once a day) were randomized into two groups. Vildagliptin groupandTeneligliptin groupwere added with Vildagliptin 50mg, twice a dayand Teneligliptin 20mg, once a day as an add-on therapy respectively.

Results: Reductions in FPG, 2 hours PPG and HbA1c in the vildagliptin groupwere comparable with the teneligliptin group. Patients in both groups showed similar tolerability.

Conclusion: Teneligliptin showed glycaemic reduction comparable to that of vildagliptin when given as a dual therapy with metformin or triple therapy with metformin and glimepiride. Teneligliptin appeared to be more potent than vildagliptin based on its glucose-lowering effects.

Keywords: Metformin, Teneligliptin, Vildagliptin, Type2Diabetes mellitus, HbA1c

INTRODUCTION

Diabetes mellitus (DM) is an established risk factor for cerebrovascular and peripheral arterial diseases.[1] Being a complex and chronic illness, it requires continuous medical care with multifactorial risk-reduction strategies beyond glycaemic control.[2] Several distinct types of diabetes are caused by a complex interaction of genetics and environmental factors. Many drugs have also been linked with an increased risk of development of type 2 DM.[3,4]

It was estimated in 2017 that 451 million adults worldwide had diabetes and approximately 90% of these patients have type 2DM. [5,6] According to the International Diabetes Federation (IDF) 2017 report, China has the highest number of people with diabetes. This is closely followed by India with 72.9 million people with diabetes.

The recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes recommends the use of relatively newer drugs such as sodium-glucose cotransporter 2 inhibitors (SGLT-2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and dipeptidyl peptidase 4 inhibitors (DPP-4i) in combination with metformin and lifestyle adjustments.[7]

Metformin has been the first-line therapy for type 2DM andsulfonylureas, acting as insulin secretagogues are the usually next therapeutic step when patients do not achieve or maintain glycemic control on metformin alone. [8,9]

However, the function of beta continues to worsen over time in most of the patients with type 2DM leading to the deterioration of beta cells which is responsible for the failure in achieving sustained glycemic control. Gliptins (DPP-4i) are a relatively new class of antidiabetic drugs possessing several clinical advantages like a negligible risk of hypoglycemia and weight neutrality.[10,11]

Vildagliptin has already been shown to be an effective and clinical studies have shown that vildagliptin in combination with metformin resulted in better glycemic control than high-dose metforminalone.[12,13] Teneligliptin is a novel DPP-4 inhibitor approved recently for the management of type 2 DM in some countries, namely, Japan (2012), South Korea (2014), and India (2015).[14,15,16] Teneligliptin is still a relatively new drug and published clinical data related to this drug are sparse.

The present study aimed compared the efficacy and safety profiles of two gliptins, vildagliptin and teneligliptin, in patients with type 2 diabetes as add-on therapy to traditional first-line oral antidiabetic drugs.

STUDY POPULATION

Study design
This was a randomized, prospective, open-labeled, parallel-group, single-center, 24 weeks clinical study of patients who have attended a diabetic clinic of the tertiary level hospital in India with type 2 DM from March 2016 to September 2017.

Inclusion criteria
The patients, age 20–75years if they had type 2DM with inadequate glycemic control, defined as glycated hemoglobin (HbA1c) of 7.5% to 11.0%, treated with conventional first-line oral antidiabetic drugs (metformin, 500-850 mg twice a day or metformin 500-850, mg twice a day withglimepride2-3 mg once a day) were administered with teneligliptin or vildagliptin as add on therapy.

Exclusion criteria
Patients on oral antidiabetic agents other than metformin and glimepiride, patients with significant kidney diseases, abnormal liver function tests (alanine transaminase [ALT] >2× upper limit of normal [ULN], aspartate transaminase >2× ULN or total bilirubin >2× ULN and/or direct bilirubin >ULN) were excluded from the study. Patients with other significant systematic illnesses, pregnant and lactating women were also excluded.

Eligible patients were randomized into two groups (Vildagliptin group and Teneligliptin group) according to the table generated by random allocation software. The randomization was generated having 20 patients in each block to minimize the disparity between the two groups.

Ethical clearance
The study protocol was approved by the Institutional Ethics Committee (IEC) and the study was also registered with the Clinical Trial Registry of India(ref No: ctri /2017/02/007766).

Informed and written consent was obtained from all patients before enrolling them in the study group. Diagnosis of diabetes was made according to criteria for the diagnosis of diabetes mellitus of American Diabetes Association, 2017[1].

Pharmacotherapy
Group1 (Vildagliptin group): Vildagliptin (50mg, twice a day) was administered as add-on therapy to all the patients of Vildaglitin group(n=82) who were already receiving Metformin (500mg/850mg, twice a day) with or without Glimepiride (2mg/3mg, once a day).

Group2(Teneligliptin group): Teneligliptin (20mg, once a day**)** was administered as add-on therapy to all the patients of the teneligliptin group (n=81) who were already receiving Metformin (500mg/850mg, twice a day) with or without Glimepiride (2mg/3mg, once a day).

Follow up of patients
The patients of all groups were followed up in 6,12,18 and 24 weeks. They were advised to consult the endocrinologist/treating physician/investigator for any queries or adverse effects of medicines if occur during the treatment period. All the patients were recommended to take a diabetic diet as advised by the registered dietician of the hospital.

Efficacy assessment
The primary endpoint was the efficacy profile for each gliptin in terms of reduction in fasting blood glucose (FBG), postprandial plasma glucose (PPG) and, HbA1c at 12, and 24weeks from baseline values. The secondary endpoint was to determine the safety and tolerability profiles of teneligliptin and vildagliptin by assessing adverse effects.

Safety assessment

All adverse events experienced by a patient or observed by the endocrinologist/treating physician/investigator were recorded at each visit. Safety was assessed based on the incidence of Adverse events (AEs) and hypoglycemic episodes. Regarding hypoglycemia, patients were asked to describe their experience of hypoglycemic episodes. Any patient who reported a self-monitored blood glucoselevel <70 mg/dl, with or without symptoms of hypoglycemia was considered to have a hypoglycemic episode. Safety assessment was done using Naranjo's Adverse Drug Reaction Probability Scale.[17] The severity of the reaction was assessed using Adverse Drug Reaction Severity Assessment Scale: Modified Hartwig and Siegel.[18] Additional routine laboratory safety tests like Complete blood count (CBC), Renal function tests (blood urea and serum creatinine), Liver function tests (LFT), Lipid Profile, and electrocardiogram (EKG) etc., were also performed wherever required.

STATISTICAL ANALYSIS

For descriptive statistics; frequency, percentage, mean ± standard deviationwas used to analyzethe study results.Intra-group and inter-group analysis of the two groups was done using repeated measure ANOVA (RM-ANOVA).P< 0.05 was considered as statistically significant. Statistical analysis was done using Statistical Package for Social Sciences (SPSS-23) software and charts were prepared using Microsoft Excel 2013

OBSERVATIONS AND RESULTS

A total number of 227 patients were enrolled, out of which 64 patients (33 patients of Vildagliptin group and 31 patients of Teneligliptin group), failed to complete the study. A total of 163 patients, 82 patients from Vildagliptin group and 81 patients from Teneligliptin group completed study.

Figure1: Flow chart showing the distribution of patients

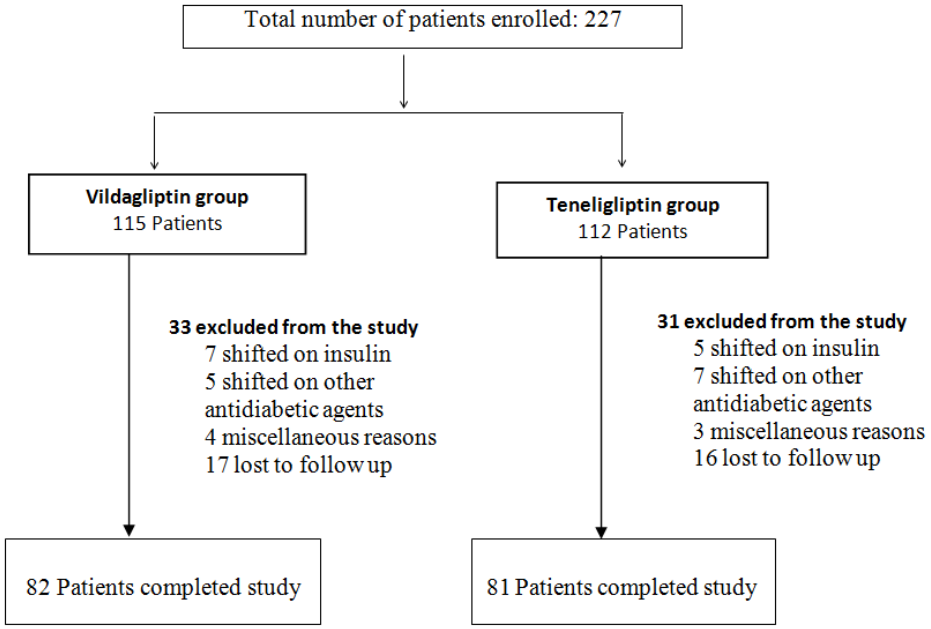

Table 1: Demographic profile

Parameters	**Vildagliptin group** (n=82 Mean ± SD	**Teneligliptin group** (n=81) Mean ± SD
Age (years) Mean ± SD	50.07 ± 10.38	50.07 ± 10.38
Gender Male (n=72) Female (n=91)	 33 (40.24%) 49 (59.76%)	 39 (48.15%) 42 (51.85%)
BMI (kg/m^2)	27.87 ± 3.07	27.75 ± 3.75
Lipid profile parameters (mg/dL) Total Cholesterol Triglycerides HDL LDL VLDL	 179.85 ± 29.86 165.37 ± 35.98 41.26 ± 5.75 98.48 ± 19.33 28.07 ± 8.92	 180.03 ± 28.43 176.41 ± 27.14 41.79 ± 5.83 102.86 ± 19.35 30.52 ± 9.00

Liver Function Test		
Total bilirubin(mg/dL)	0.67 ± 0.17	0.67 ± 0.15
Aspartate transaminase (I.U.)	18.41 ± 2.08	18.76 ± 5.91
Alanine transaminase (I.U.)	37.43 ± 3.08	21.87 ± 5.23
Alkaline Phosphatase (I.U.)	84.20 ± 9.15	89.75 ± 2.06
Renal Function Test (mg/dL)		
Blood Urea	26.47 ± 7.12	21.50 ± 6.67
Serum Creatinine	0.88 ± 0.13	0.87 ± 0.15
Glycemic Parameters		
Fasting Plasma Glucose(mg/dL)	148.64 ± 49.99	157.61 ± 45.67
Post Prandial Glucose(mg/dL)	222.59 ± 66.88	228.65 ± 65.16
HbA1c(%)	8.20 ± 1.14	8.45 ± 1.24

The age of patients varies from 25 years to 75 years. Aspirin and atorvastatin, once a day, were also prescribed to 43 patients of the vildagliptin group and 37 patients of the teneligliptin group. 32 patients of the vildagliptin group and 28 patients of the teneligliptin group were on angiotensin receptor blockersand hydrochlorothiazide once a day, respectively. 9 patients in the vildagliptin group and 12 patients in the teneligliptin group were on metoprololonce a day.

EFFICACY OUTCOMES

Fasting plasma glucose (FPG))

Acomparative analysis shows that the meanbaseline valuesof FPG in the vildagliptin Group and Teneligliptin Group were statistically insignificant ($p>0.05$).The reduction in mean values of FPG at 12 and 24 weeks, when compared to baseline values was significant within the groups ($p<0.001$). However, the reduction in FPG in Vildagliptin Group and Teneligliptin Group at 12 and 24 weeks when compared with values of two groups (Vildagliptin Group and Teneligliptin Group) was found to be statistically insignificant ($p>0.05$) [Table 2].

When %reduction in FPG (0-24weeks) was calculated and it was greater in the teneligliptin group than those in the vildagliptin group.

Table 2: Mean Fasting Plasma Glucose (FPG) Levels

Groups (n=163)	Baseline (mg/dL) Mean ± SD	12 weeks (mg/dL) Mean± SD	24weeks (mg/dL) Mean ± SD	%Reduction (0-24weeks)	Intragroup comparison	Intergroup comparison
Vildagliptin Group (n=82)	148.64 ± 49.99	120.60± 30.59	102.60± 24.70	30.97	p<0.001	p>0.05
Teneligliptin Group (n=81)	157.61± 45.67	121.65± 35.52	108.18± 29.31	31.36	p<0.001	p>0.05

Values are expressed as Mean ± SD; Intra-group comparison shows highly significant values ($p<0.001$) at all-time points when compared to baseline value of respective group. Values were non-significant with $p>0.05$ when inter-group comparison was made.

2 Hours post prandial plasma glucose (2h PPG)

The mean values at zero weeks (baseline values) of 2hour PPG in the vildagliptin group and the teneligliptin group were statistically insignificant ($p>0.05$).

The reduction in mean values of 2 hours PPG, when compared to baseline values, was significant at 12, and 24 weeks within the groups ($p<0.001$). However, the reduction in 2 hours PPG in Vildagliptin Group and Teneligliptin Group at 12, and 24 weeks when compared with baseline values of two groups was found to be statistically insignificant ($p>0.05$) [Table 3].

Table 3: Mean 2 hours Post Prandial Plasma Glucose (2h PPG) Levels

Groups (n= 163)	Baseline (mg/dL) Mean ±SD	12 weeks (mg /dL) Mean ±SD	24 weeks (mg/dL) Mean ± SD	% Reduction	Intragroup comparison	Intergroup comparison
Vildagliptin Group (n= 82)	222.59 ± 66.88	183.01 ± 44.56	162.19 ± 32.26	27.13	p < 0.001	p > 0.05
Teneligliptin Group (n= 81)	228.65 ± 65.16	189.32 ± 45.95	166.40 ± 43.84	27.22	p < 0.001	p > 0.05

Values are expressed as Mean ± SD; Intra-group comparison shows statistically significant values (p<0.001) at all-time points when compared to baseline value of respective group. Values were non-significant with p > 0.05 when inter-group comparison was made.

Glycosylatedhaemoglobin (HbA1c)

Thebaseline valuesof HbA1c when compared in the two groups were found to be statistically insignificant (p>0.05).
The reduction in mean values of HbA1c, when compared to baseline, was significant, at all times points (at 12 and 24 weeks) within the groups (p<0.001). However, when the reduction in the mean values of HbA1c between the two groups at 12 and 24 weekswere compared with each other it was found to be statistically insignificant (p>0.05) [Table 4].

Table 4: Mean Glycosylated Haemoglobin(HbA1c)

Groups (n=163)	Baseline (%) Mean ± SD	12 weeks (%) Mean ± SD	24 weeks (%) Mean ± SD	Percentage reduction at 24wks	Intragroup comparison	Intergroup comparison
Vildagliptin Group (n=82)	8.20 ± 1.14	7.56 ± 0.97	6.94 ± 0.84	15.36%	p < 0.001	p > 0.05
Teneligliptin Group (n=81)	8.45 ± 1.24	7.50 ± 1.02	6.80 ±1.00	19.50%	p < 0.001	p > 0.05

Values are expressed as Mean ± SD; Intra-group comparison shows highly significant values (p < 0.001) at all-time points when compared to baseline value of respective group. Values were non-significant with p > 0.05 when inter-group comparison was made.

Renal function test

At zero weeks the mean blood urea (mg/dL) was 26.47 and 21.50 in Vildagliptin group and Teneligliptin group respectively. After 24 weeks of treatment, mean blood urea was 27.18 and 21.77 respectively. The change in mean values of blood urea when compared to baseline, was nonsignificant, at all times points groups (p>0.05).

At zero weeks, the mean serum creatinine was 0.88 and 0.87 in Vildagliptin group and Teneligliptin group respectively. After 24 weeks of treatment, mean serum creatinine was 0.86 and 0.86 respectively. The change in mean values of serum creatinine when compared to baseline, was not significant at 12 and 24 weeks in the two groups (p>0.05)

Liver function test

At baseline (zero week), the mean total bilirubin (mg/dL) was, 0.67 and 0.67 in Group 1 and Group 2 respectively. After 24 weeks of treatment, mean total bilirubin (mg/dL) was 0.66 and 0.69 respectively. The change in mean values of total bilirubin, when compared to baseline, was not significant within the groups (p> 0.05).

At baseline (zero week), the mean Aspartate Transaminase (AST), Alanine Transaminase (ALT), and Alkaline Phosphatase (ALP) were 18.41 and 18.76, 37.43, and 21.87, 84.24 and 84.24 (IU/L) in Group 1 and Group 2 respectively. After 24 weeks of treatment, mean AST, ALT and ALP were 17.51 and 18.29, 36.24 and 24.74, 89.66 and 82.04 respectively. The changes in mean values of AST, ALT and ALP, when compared to baseline were insignificant within the groups (p> 0.05).

Lipid profile

At zero week, the mean total cholesterol (mg/dL) was 179.85 and 180.03 in Group 1 (vildagliptin group) and Group 2 (teneligliptin group)respectively. After 24 weeks of treatment, mean total cholesterol was 177.19 and 175.45 in

vildagliptin group and teneligliptin group respectively. The change in mean values of total cholesterol, when compared to baseline, was not significant, within the groups and between the groups (p> 0.05). At 0 week, the mean triglyceride (mg/dL) was 165.37 and 176.41 in Group 1 and Group 2, respectively. After 24 weeks of treatment mean triglycerides (mg/dL) was 167.35 and 170.29 respectively. At baseline, the mean HDL, LDL, and VLDL were 41.26 and 41.79, 98.48 and 102.86, 28.07 and 30.52(mg/dL) in Group 1 and Group 2 respectively. After 24 weeks of treatment, mean HDL, LDL and VLDL were, 39.58 and 40.30, 93.48 and 95.82, 29.74 and 30.53 (mg/dL) respectively. The changes in mean values of HDL, LDL and VLDL, when compared to baseline were insignificant within the groups (p> 0.05).

Safety: In Group 1, 17 patients experienced adverse events and in Group 2, 20 patients experienced adverse events (Table 27). The most commonly observed adverse event was nausea, followed by headache. Other adverse events observed were vomiting and decreased frequency of bowel movement (Table 28). No adverse event required discontinuation of therapy. The results showed that the occurrence of adverse events was not significantly different between Group 1 and Group 2. The adverse events were of mild to moderate in severity according to Modified Hartwig and Siegel scale, in all of the cases. On Naranjo's ADR Probability Scale, the events were possible in 14 cases and probable in 3 cases in Group 1, while possible in 17 cases and probable in3 cases in Group 2. The occurrence of adverse events was similar in the two groups.

DISCUSSION

Diabetes mellitus is a growing health problem. A patient-centered approach should be utilized to guide the choice of pharmacological agents considering factors such as efficacy, cost, potential side effects, comorbidities, and patient preferences. [19]

Metformin, the first-line therapy for type 2 DM [8] has been shown to delay the progression of type 2 DM, reduce the risk of complications and mortality rates in patients.[20] The patients with HbA1c between 7-8% while on metformin therapy if added with gliptin to the already existing dose of metformin rather than increasing the dose of metformin, the HbA1c reduction is greater than up-titrating the dose of metformin.[21] Sulfonylureas may be the subsequent therapeutic option when patients do not achieve or maintain glycemic control on metformin alone.[9] Dual-combination therapy with sulfonylureas and metformin sometimes may not achieve glycemic control.[22] Hence, additional antidiabetic agents are needed, that can be added to the dual combination of sulfonylurea and metformin to achieve and maintain glycemic target.

DPP-4 Inhibitorswhen administered to patients inadequately controlled with metformin cause a considerable improvement in HbA1c with twice the number of patients achieving an HbA1c of <7% compared to metformin alone.[23]Bosi E et al. (2007), conducted a 24 weeks study on patients with type 2 diabetes mellitus inadequately controlled with stable doses of metformin (≥ 1500mg/day) where vildagliptin was added as an add-on therapy to patients in doses of 50mg/day or 100mg/day. There was a reduction in HbA1c of -0.7% and -1.1% at 50mg and 100mg doses, respectively. [24]

Ahren B et al. (2005) conducted a 52-week trial where vildagliptin (50mg) was given to patients already treated with metformin (1500–3000mg daily), and there was a reduction in HbA1c at 12 weeks by 0.6%.[25]

Kim MK et al. (2015) conducted a 16-week study where teneligliptin (20mg, ONCE A DAY), as an add on therapy to stable doses of metformin (>1000mg/day) improved HbA1c (-0.78%) and Fasting plasma glucose (-22.42mg/dl) in Korean patients with type 2 DM.[26]

In the current study, vildagliptin (100mg/day) and teneligliptin (20mg/day) have been added as add-on therapy in patients with type 2 DM, inadequately controlled on stable doses of metformin (1000 mg to 1700mg/day). Results showed a change in mean HbA1c of -0.92% and -1.17 % from the baseline in the Vildagliptin Group receiving vildagliptin (100mg/day) and metformin at doses of 850mg and 500mg twice daily, respectively. In the Teneligliptin Group, teneligliptin (20mg, once a day) showed a reduction in HbA1c of -1.21% and -1.42% when added to metformin at doses of 850mg and 500mg twice a day, respectively (Table 4).

In previous studies, gastrointestinal side effects were seen which were mild. Hypoglycemia was reported in 0.6% of patients receiving vildagliptin and 0.4% of patients receiving metformin.[24] Our study results showed adverse events similar in profile to the previous studies and no episodes of hypoglycemia were reported in either of the groups receiving vildagliptin and teneligliptin as dual therapy. Kadowaki K et al. (2014) also concluded in their 12 weeks study that teneligliptin was effective and well-tolerated when combined with a stable dose of glimepiride on 194 Japanese patients with type 2 DM.[27]

A majority of studies showed no significant difference in the change in HbA1c, fasting plasma glucose and, postprandial plasma glucose between the gliptins. In our study, the results were similar to the previous studies and no

significant difference in the efficacy of vildagliptin and teneligliptin was seen when given as add-on therapy to metformin.

Our results were consistent with previous studies, which concluded that no significant adverse events were seen with the co-administration with metformin, sulfonylureas and, gliptins.[28]We did not use a higher dose of sulfonylureas and no episodes of hypoglycemia were reported on combining these three drugs, however, reduction in the dose of sulfonylureas is usually recommended when gliptin is added to sulfonylureas since its pharmacodynamics interaction with sulfonylureas might result in a high risk of hypoglycemia.[29]

We found that the reduction in HbA1c, FPG, 2 hours PPG was greater in the group receiving teneligliptin. As mentioned in the previous studies this may be explained by the structural advantage of teneligliptin, which binds to the S2 extensive subsites via an 'anchor lock domain', and this interaction may be related to the increased strength of inhibition, the residence time for binding to DPP-4, and the long duration of action in vivo.[14]

Teneligliptin has a pharmacokinetic advantage of a longer half-life of 24.2 hours and causes more than 90% inhibition of the DPP-4 activity even after 24hours, which favors once a day regime for this drug.[30]

CONCLUSION

In our study, the comparison was done between vildagliptin and teneligliptin as an add-on therapy to stable doses of metformin with or without glimepiride. Teneligliptin showed glycemic reduction comparable to that of vildagliptin when given as dual therapy with metformin or triple therapy with metformin and glimepiride. Teneligliptin appeared to be more potent than vildagliptin based on its glucose-lowering effects. The current study has further added the evidence that teneligliptin at a dose of 20 mg/day is effective on the related parameters of glycemic control in type 2 DM patients and it is non-inferior to vildagliptin. More trials of direct comparisons between gliptins are needed as they differ structurally.

Conflict of interest: No conflicts of interest exist.

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