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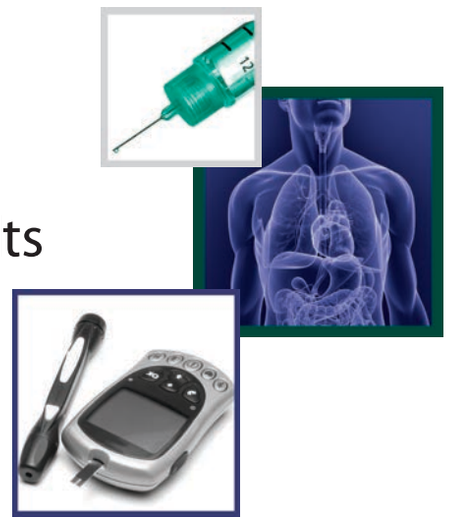

Canagliflozin for the treatment of adults with Type 2 diabetes

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Practice Points

- Canagliflozin can be initiated at a dose of 100 or 300 mg once daily, preferably before breakfast.
- The initial tolerability profile of canagliflozin suggests that genital fungal infection may appear, particularly in women, and must be treated accordingly. There is no need to discontinue medication. It could be useful to screen for genital fungal infection and treat before starting canagliflozin. Urinary tract infections can also develop and must be treated accordingly. Transient polyuria, pollakiuria, thirst and/or postural dizziness may also be present.
- Drugs such as rifampin, phentoin, phenobarbital and ritonavir may decrease the action of canagliflozin. SGLT2 inhibitors such as canagliflozin become ineffective in severe renal impairment.

SUMMARY Canagliflozin is a competitive, reversible and potent inhibitor of SGLT2 that lowers the renal threshold for glucose and consequently increases urinary glucose excretion in people with Type 2 diabetes with a blood glucose level above 70–90 mg/dl. Its oral administration in daily doses of 100 and 300 mg in monotherapy, dual therapy or triple therapy including insulin produces a mean HbA1c reduction of 0.7 and 0.85%, respectively, when compared with placebo, a similar reduction to sitagliptin and glimepiride. There is also a modest reduction in weight with both doses. The main adverse effects are genital fungal infections, particularly in women, and, less frequently, urinary tract infections.

The number of people with Type 2 diabetes mellitus (T2DM) is increasing beyond our worst expectations, and the socioeconomic burden of diabetic complications is overloading the health systems. A call for earlier and more effective glucose control has led investigators to search for effective and safe antidiabetic drugs, particularly those that do not increase weight or cause hypoglycemia. The use of SGLT2 inhibitors as antihyperglycemic agents has emerged from the interesting observation that phlorizin, a natural product isolated from the root bark of the apple tree, can cause glucosuria in partially pancreatectomized rats and correct hyperglycemia [1]. Its mechanism of action is related to inhibition of the glucose transporter SGLT2, which is responsible for more than 90% of the renal glucose reabsorption in the proximal convoluted tubule. Although phlorizin never reached the human experimental phase, it was a proof of concept that led to the development of highly specific SGLT2 inhibitors. Since glucosuria is a marker of uncontrolled diabetes, there has been concern about inducing it by inhibiting SGLT2, but people with mutations of *SLC5A2* (the SGLT2-coding gene) remain

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healthy, apart from developing what has been called familial renal glucosuria, and eliminate glucose up to 100 g/day [2]. People with T2DM may have increased SGLT2 activity as demonstrated in cultures of renal proximal cells, which expressed significantly more SGLT2 (and GLUT2) in response to hyperglycemia compared with cells from healthy control subjects [3]. Whether SGLT2 inhibitors are correcting a defect in T2DM, taking advantage of a physiologic mechanism or both is a matter for debate. The purpose of this review is to summarize the experimental and clinical data available on canagliflozin (CANA), a SGLT2 inhibitor that was submitted to the US FDA Endocrinologic and Metabolic Drugs Advisory Committee in January 2013 as an adjunctive treatment to diet and exercise alone, or coadministered with other antihyperglycemic agents to improve glycemic control in adults with T2DM [101], and was recently approved by the FDA under the trade name INVOKANA™ (Janssen Pharmaceuticals, Inc., NJ, USA).

Dosage & administration

A dose-dependent effect of CANA can be observed at daily doses as low as 50 mg, but Phase I and II studies have shown that 300 mg provides maximal reductions of the renal threshold for glucose (RT_G) over 24 h and 100 mg provides it for up to 13 h, with continuing submaximal but substantial reductions over the remaining 11 h. Since the antihyperglycemic efficacy of CANA is mainly dependent on the reduction of the RT_G, which leads to increased urinary glucose excretion (UGE), only daily doses of 100 and 300 mg have been selected for Phase III studies and submitted to the FDA for clinical use. The mean terminal plasma elimination half-life is approximately 11 and 13 h for these doses, respectively, and the pooled data support once-daily dosing for both. The oral bioavailability of CANA in humans is not interfered with by food ingestion but CANA has a transient effect on intestinal glucose absorption, particularly with the 300-mg dose, and this effect can be optimized when given before the morning meal [101].

Preclinical data

CANA is a C-glucosides 4 bearing a heteroaromatic ring with enhanced stability compared with O-glucosides. It is a thiophene derivative 4b-3 (TA-7284/JNJ-28431754) and has shown pronounced antihyperglycemic effects in high-fat diet fed KK mice [4].

CANA is a competitive, reversible and potent inhibitor of SGLT2 that lowers the RT_G and consequently reduces the reabsorption of filtered glucose and increases the UGE. CANA can lower the RT_G in Zucker diabetic fatty rats receiving a high glucose infusion from approximately 415 mg/dl to 94 mg/dl. UGE increased linearly in proportion to blood glucose only above that threshold, even if the blood glucose had been lowered first below the RT_G with insulin. When the rats were treated with CANA over 4 weeks, a significant decrease was observed in HbA1c and area under the curve for blood glucose during an oral glucose tolerance test when compared with vehicle-treated animals. In diet-induced obese mice treated with CANA for 4 weeks, body weight was significantly lower when compared with vehicle-treated animals, and this was associated with a tenfold increase in UGE, while no change was observed in food intake. Similar results were found in Zucker fatty rats treated with CANA for 3 weeks where the weight of epididimal fat and liver was also significantly lower [5].

CANA is also an inhibitor of SGLT1, although the potency is 160-times less compared with inhibition of SGLT2 [101]. SGLT1 is highly expressed in the intestine and is mostly responsible for intestinal glucose and galactose absorption [101].

Clinical pharmacology

After oral administration, CANA maximal concentration (T_{max}) is reached at 1–2 h with 100- and 300-mg doses, and the steady state is reached after 4–5 days. In plasma, more than 98% of CANA binds to albumin and α-acid glycoprotein and it is mainly metabolized through *O*-glucuronidation. Approximately 60% of the drug is eliminated in the feces (42% as CANA and the rest as metabolites). The other main route of elimination is urinary, where less than 1% is recovered as unchanged drug and the rest as metabolites. Variations in age, sex, race, body weight, diabetes status and genetic polymorphisms in the *UGT1A9*3* allele have no meaningful effect on the disposition of CANA. In therapeutic doses, the potential for clinically significant interactions with other drugs is low, but drugs affecting UGT enzymes responsible for *O*-glucuronidation (rifampin, phenytoin, phenobarbital and ritonavir) may decrease the

action of CANA. CANA at doses ≥200 mg reduce the mean 24-h RT_G to 50–60 mg/dl in healthy subjects and 70–90 mg/dl in people with T2DM. At that RT_G, there is no UGE and, therefore, the potential risk of drug-induced hypoglycemia is low [101].

In healthy subjects, CANA increases the 24-h urine volume to 0.9 l and the 24-h mean UGE to 70 g when compared with placebo. The drug was given before breakfast and a short-term effect was observed with doses >200 mg on postbreakfast blood glucose and serum insulin, which was not accounted for by UGE, raising the possibility that CANA has a direct effect on intestinal glucose absorption [6]. To explore further the effect of CANA on intestinal glucose absorption, a two-period crossover study was performed to assess effects of a single 300-mg dose on intestinal glucose absorption using a dual tracer method. CANA delayed and reduced the cumulative appearance in plasma of oral glucose (RaO) by 31 and 20% at 1 and 2 h, respectively, compared with placebo, suggesting that intestinal levels of the drug may be sufficiently high to inhibit intestinal SGLT1 transiently [7]. This was also observed in a crossover study in patients with T2DM inadequately controlled on metformin (MTF). CANA 150 and 300 mg increased UGE and lowered fasting plasma glucose, but only the 300 mg dose lowered the 2-h postprandial glucose by 16% and a further 19% when given twice, suggesting, again, a nonrenal effect probably caused by local/transient intestinal SGLT1 inhibition from high intraluminal CANA levels during drug absorption [8].

■ Clinical evidence in T2DM patients

Eight Phase III double-blind, randomized clinical trials have tested CANA 100 and 300 mg against placebo (four trials) or active comparator (four trials) in general population with T2DM. These studies have included 5742 patients followed for a mean of 30 weeks (standard deviation: 16 weeks). At present, only three have been published [9–11] and the rest have been presented at international diabetes meetings [12–16] and/or included in the briefing document [101]. CANA has also been tested in three special populations with T2DM (elderly, renal impairment and high cardiovascular risk [17,18,101]).

■ Glucose control

Monotherapy with CANA 100 and 300 mg was compared with placebo in subjects with T2DM inadequately controlled with diet and exercise. Their mean age was 55.4 years and median disease duration was 3 years. HbA1c decreased significantly with both doses and, consequently, the proportion of subjects reaching an HbA1c <7% was significantly higher **(Table 1)** [9,12,13]. A substudy was conducted in subjects with an HbA1c of 10.1–12.0% who only received active treatment. The mean HbA1c changes from baseline were -2.1 and -2.6% with 100 and 300 mg, respectively [101].

As add-on therapy in T2DM subjects inadequately controlled with MTF, CANA 100 and 300 mg have been compared with placebo [10], sitagliptin [10] and glimepiride [14]. Both doses of CANA are superior to placebo and CANA 300 mg is superior to glimepiride

Table 1. Effect of canagliflozin treatment on glucose control in patients with Type 2 diabetes mellitus.

Previous treatment	Patients (n)	Mean HbA1c (%)	Follow-up (weeks)	HbA1c reduction from baseline; % (proportion achieving HbA1c <7%)			Ref.
				Comparator	CANA 100 mg	CANA 300 mg	
Diet and exercise	584	8.0	26	Placebo: +0.14 (21%)	-0.77* (45%)	-1.03* (62%)	[9,12,13]
MTF	322	7.8	12	Placebo: -0.22 (34%) Sitagliptin: -0.74 (65%)	-0.76* (53%)	-0.94* (72%)	[10]
MTF	1450	7.8	52	Glimepiride: -0.81	-0.82	-0.93*	[14]
MTF + SU	469	8.1	26	Placebo: -0.2 (18%)	-0.91* (43%)	-1.12* (57%)	[15]
MTF + SU	755	8.1	52	Sitagliptin: -0.66	–	-1.03*	[11]
MTF + pioglitazone	344	7.9	26	Placebo: -0.26 (33%)	-0.89* (47%)	-1.03* (64%)	[101]
Insulin ± OADs	1818	8.3	18	Placebo: +0.01 (8%)	-0.63* (20%)	-0.72* (25%)	[16]
Various AHAs in the elderly	714	7.7	26	Placebo: -0.03 (28%)	-0.6* (48%)	-0.73* (59%)	[18]
Insulin/SU with renal impairment	269	8	26	Placebo: -0.03	-0.33*	-0.44*	[17]

*$p < 0.001$ versus comparator.
AHA: Antihyperglycemic agent; CANA: Canagliflozin; MTF: Metformin; OAD: Oral antidiabetic drug; SU: Sulfonylurea.

(mean dose: 5.6 mg) in lowering HbA1c. CANA 100 mg is noninferior to glimepiride and both doses are similar to sitagliptin (100 mg) in lowering HbA1c **(Table 1)**.

In triple therapy, CANA 100 and 300 mg have been tested in patients with T2DM inadequately controlled with MTF plus sulfonylurea (SU) [15] or MTF plus pioglitazone [101], or insulin ± oral antidiabetic drugs [16]. Both doses reduced HbA1c significantly when compared with placebo. CANA 300 mg was also compared with sitagliptin as an add-on to MTF plus SU [11], and the former was superior to the latter in lowering HbA1c **(Table 1)**.

In the placebo-controlled studies/substudies, placebo-subtracted least squares mean reductions in fasting plasma glucose were seen with both the 100-mg dose (ranging from -22.4 to -37.4 mg/dl) and with the 300-mg dose (ranging from -27.7 to -48.1 mg/dl). In the two placebo-controlled studies in which all subjects had a mixed meal tolerance test, placebo-subtracted least squares mean reductions in 2-h postprandial glucose were seen with both the 100-mg dose (ranging from -38.1 to -48.1 mg/dl) and with the 300-mg dose (ranging from -47.3 to -64 mg/dl) [101].

UGE was studied in the CANA add-on to MTF study [10] and expressed as mg/mg of creatinuria (Uglucose/Ucreatinine). With placebo, the mean Uglucose/Ucreatinine was 1.9 mg/mg, with sitagliptin it was -1.9 mg/mg, and with CANA it increased to almost 62 mg/mg with the 300-mg dose (with 100 mg it increased to 51.5 mg/mg). The increase in UGE observed at week 3 persisted without evident attenuation up to week 12.

Adverse events

In all studies, the rates of serious adverse events (AEs) and AE-related discontinuations were low and similar among groups. Incidence of hypoglycemia was also low and similar among groups, except when CANA was administered to patients receiving SUs and/or insulin, where the number of patients having at least one episode was 41–95% higher than placebo. On the background of MTF and SU, the event rates of documented episodes of hypoglycemia were 2.6 and 3.4–4.1 per subject-year exposure for CANA 100 and 300 mg, respectively. On the background of insulin, the corresponding rates were 7.2 and 8.4 per subject-year exposure. Nevertheless, the number of severe hypoglycemic events was very low.

The difference in AEs with CANA versus comparator was mainly due to genital fungal infections and urinary tract infections, but all were generally mild and led to few discontinuations **(Table 2)**. Overall, 73.2% of the cases of genital fungal infections in women were treated with antifungal agents, 1.8% were treated with antibacterial agents, 5.2% were treated with both agents and 19.8% were not treated. The response to antifungal treatment appeared to be generally similar with the median time to symptom resolution only slightly longer in the CANA 300-mg group (8.7 days) relative to the CANA 100-mg (7.0 days) and the non-CANA groups (6.5 days).

Frequency of polyuria, pollakiuria, thirst and postural dizziness was also slightly higher in some studies, but not all. CANA led to small reductions from baseline in estimated glomerular filtration rate (eGFR) that were generally stable or improved with continued treatment, and this has been attributed to reduced intravascular volume (prerenal) [101].

The mean placebo-subtracted absolute increase of hematocrit was 2.3 and 2.5% with the 100- and 300-mg doses, respectively. No significant changes in serum electrolytes were observed, including serum sodium [101].

Cardiovascular safety

Low-density lipoprotein cholesterol increases slightly with CANA 100 and 300 mg (2.8 and 7.2 mg/dl, respectively, in the placebo-controlled studies dataset). In some studies where Apo B and non-high-density lipoprotein cholesterol were measured, the increases were approximately half the extent of the increases in low-density lipoprotein cholesterol. These unfavorable changes in the lipid profile may be counterbalanced by the favorable effect of CANA on high-density lipoprotein cholesterol (up to a 7% increase), blood pressure (decreases up to 6 mmHg), weight loss and glucose control. A cardiovascular meta-analysis of adjudicated events was carried out for randomized clinical trials of CANA of at least 12 weeks duration, including the ongoing 4-year CANA Cardiovascular Assessment Study (CANVAS), where 4385 subjects with prior cardiovascular disease history or risk factors for cardiovascular disease were randomized. The primary outcome was adjudicated mortality and major cardiovascular end points, including hospitalized unstable angina, which occurred in 2.1% of subjects in both groups (6305 with

CANA and 3327 controls) with a hazard ratio of 0.91 (95% CI: 0.68–1.22) [101].

■ Hepatic safety

The few cases of hepatic injury (combined criteria of ALT/AST >three-times the upper limit of nomal and bilirubin >two-times the upper limit of normal) were more frequent in patients receiving CANA (0.14 vs 0.05%), but the Hepatic Events Assessment Committee (HEAC) excluded drug causality in most of them and none have met Hy's law criteria [101].

■ Cancer safety

The 2-year rat carcinogenicity study showed an increase in Leydig cell tumors, pheochromocytomas and renal tubular cell tumors, but an extensive mechanistic toxicology program has demonstrated that the findings in rats were not relevant for human risk [101].

These and other tumors such as bladder and breast cancer have been carefully monitored in the clinical studies and only a few events have occurred (no Leydig cell tumors nor pheochromocytomas), but there has been no meaningful imbalance among the study groups [101].

Special populations

■ High cardiovascular risk

A subgroup of patients receiving insulin in the ongoing CANVAS study were analyzed at 18 weeks. The mean age was 63 years, median duration of diabetes 15 years and mean daily baseline insulin 83 IU. CANA 100 and 300 mg decreased HbA1c and body weight significantly compared with placebo **(Tables 1 & 3)**. Although the incidence of AEs was similar in the three groups including placebo, there were more AEs leading to discontinuation with CANA 300 mg (5.3%) compared with CANA 100 mg or placebo (both 1.9%). The incidence of hypoglycemia was 48–49% with CANA versus 37% with placebo [101].

■ Renal impairment

CANA 100 and 300 mg were tested in subjects with T2DM and an eGFR ≥30 and <50 ml/min/1.73 m² (stage 3 National Kidney Foundation [NKF]; eGFR measured by Modification of Diet in Renal Disease [MDRD] equation) [17]. The mean age was 69 years, the mean eGFR was 39 ml/min/1.73 m² and the median baseline albumin:creatinine ratio was

Table 2. Genital and urinary infections in patients with Type 2 diabetes mellitus treated with canagliflozin.

Previous treatment	Patients (n)	Incidence of genital fungal infections (%)						Incidence of urinary tract infections (%)			Ref.
		Female			Male						
		Comparator	CANA 100 mg	CANA 300 mg	Comparator	CANA 100 mg	CANA 300 mg	Comparator	CANA 100 mg	CANA 300 mg	
Diet and exercise	584	Placebo: 3.8	12.3	12	Placebo: 0	2.5	5.6	Placebo: 4.2	7.2	5.1	[9,12,13]
MTF	322	Placebo: 3	25	17.2	–	–	–	Placebo: 6	3	4	[10]
MTF	1450	Glimepiride: 3.7	14.3	23.8	Glimepiride: 1.1	6.7	8.3	Glimepiride: 4.4	6.4	6.4	[14]
MTF + SU	469	Placebo: 5	16	21.7	Placebo: 1.3	6.6	3.4	Placebo: 5.1	6.4	5.8	[15]
MTF + SU	755	Sitagliptin: 4.3	–	15.3	Sitagliptin: 0.5	–	9.2	Sitagliptin: 4.0	–	5.0	[11]
Insulin ± OADs	1818	Placebo: 2.2	11.8	9.9	Placebo: 0.5	4.0	8.3	Placebo: 2.1	2.3	3.4	[16]
Various AHAs in the elderly	714	Placebo: 4.3	18.8	17.8	Placebo: 0	3.2	6.2	Placebo: 5.1	5.8	8.1	[18]
Insulin/SU with renal impairment	269	Placebo: 0	6.3	4.9	Placebo: 0	1.7	2.1	Placebo: 5.6	5.6	7.9	[17]

AHA: Antihyperglycemic agent; CANA: Canagliflozin; MTF: Metformin; OAD: Oral antidiabetic drug; SU: Sulfonylurea.

Table 3. Comparator-adjusted effect of canagliflozin treatment on weight in patients with Type 2 diabetes mellitus.

Previous treatment	Patients (n)	Mean BMI (kg/m^2)	Follow-up (weeks)	Weight reduction (%)		Comparator	Ref.
				CANA 100 mg	CANA 300 mg		
Diet and exercise	584	31.7	26	-2.2*	-3.3*	Placebo	[9,12,13]
MTF	322	31.5	12	-1.5*	-2.3*	Placebo	[10]
MTF	1450	31	52	-6.0	-6.6	Glimepiride	[14]
MTF + SU	469	33	26	-1.4*	-2.0*	Placebo	[15]
MTF + SU	755	31.6	52	–	-2.8	Sitagliptin	[11]
Insulin ± OADs	1818	33.8	18	-1.9*	-2.4*	Placebo	[16]
Various AHAs in the elderly	714	–	26	-2.3	-3.0	Placebo	[18]
Insulin/SU with renal impairment	269	33	26	-1.5	-1.8	Placebo	[17]

*p < 0.001 versus comparator.
AHA: Antihyperglycemic agent; CANA: Canagliflozin; MTF: Metformin; OAD: Oral antidiabetic drug; SU: Sulfonylurea.

30 µg/mg. Most subjects were on insulin (74%) and 31% were on SU. Both doses decreased HbA1c significantly at week 26 versus placebo (Table 1) and there was also a slight decrease in weight (Table 3). Systolic blood pressure was reduced, particularly with CANA 300 mg (-6.1 mmHg vs placebo). Serious AE and AE-related discontinuation rates were similar among the three groups. Both doses showed increases in serum creatinine (9–10% vs 4% with placebo) and the changes in eGFR were greater than placebo (-10 vs -3%). Follow-up eGFR information was obtained in all subjects who discontinued due to renal-related AEs. A high proportion of these subjects had follow-up eGFR values that were at baseline or only modestly below baseline levels – with a similar small proportion in the CANA and non-CANA groups having persistent decreases [101]. Median albumin:creatinine ratio was reduced with CANA 100 and 300 mg compared with placebo (-21.6 and -12.4 vs -2.5%). Although CANA seems safe and effective in patients with moderate renal impairment, it is expected that gliflozines lose efficacy when glomerular filtration of glucose decreases to a critical point [17]. Although efficacy and safety of CANA has not been tested in patients with NKF stages 4 and 5, it should not be used in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2), end-stage renal disease or in patients on dialysis, because it would not be effective [101].

■ Elderly

In subjects aged 55–80 years (mean: 63.6 years) who were inadequately controlled with antihyperglycemic agents, including MTF (85%), SUs (49%) and insulin (33%), CANA 100 and 300 mg decreased HbA1c significantly compared with placebo (Table 1). Rates of serious AEs and AE-related discontinuations were low across groups. Hypoglycemia was discretely higher with CANA in patients on antihyperglycemic agents associated with hypoglycemia (43 and 47 vs 38% with placebo). There were no discernable changes in bone density seen at the spine, hip or distal forearm by dual energy x-ray absorptiometry, although small changes were observed in bone resorption and formation markers [18].

■ Body weight changes

In all studies, there was a modest decrease in body weight compared with placebo, sitagliptin and glimepiride. Weight actually increased with the SU (Table 3).

In two studies, a body composition analysis was conducted in a subset of subjects to determine the relative contributions of weight loss from fat and lean mass by dual-energy x-ray absortiometry [19]. The results demonstrated that the reduction with CANA in fat mass was approximately twice the reduction in lean mass, accounting for more than two-thirds of total weight loss. Abdominal fat distribution was assessed by CT scans, which showed slightly greater changes in the amount of visceral adipose tissue than in subcutaneous adipose tissue, particularly with CANA 300 mg [19].

■ β-cell function

In two studies [20,21], β-cell function was evaluated in a subset of patients by modeling in a multiple-meal test [22]. The authors concluded that CANA improved β-cell function.

When added to MTF, CANA 100 and 300 mg increased β-cell function by 41% (95% CI: 19–63) and 51% (95% CI: 28–73), respectively. Insulin secretion rate increased by 74–77% and β-cell glucose sensitivity by 48%. The authors concluded that CANA improved β-cell function by approximately 50% [20]. When added to MTF plus SU, the changes in β-cell function and β-cell glucose sensitivity were not statistically significant, but the insulin secretion rate increased significantly by approximately 50–60% [21].

Financial & competing interests disclosure

PJ Aschner has served on the advisory board of AstraZeneca, Eli Lilly & Co., GlaxoSmithKline, Janssen, Merck, Sharpe & Dohme, Novartis and Sanofi, and on the speaker's bureau for AstraZeneca, Eli Lilly & Co., Boehringer, Merck, Sharpe & Dohme, Novartis, Sanofi and Novo Nordisk. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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