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BRIEF REPORT

Efficacy and Safety of Sitagliptin Compared with Dapagliflozin in People ≥ 65 Years Old with Type 2 Diabetes and Mild Renal Insufficiency

Annaswamy Raji · Zhi Jin Xu · Raymond L. H. Lam · Edward A. O'Neill · Keith D. Kaufman · Samuel S. Engel

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ABSTRACT

Introduction: Older patients with type 2 diabetes (T2D) are at increased risk of diabetic nephropathy and mild renal insufficiency. This analysis compared the anti-hyperglycemic efficacy and safety of sitagliptin with dapagliflozin in patients ≥ 65 years of age with T2D and mild renal insufficiency.

Methods: This was a post hoc analysis of data from 410 patients ≥ 65 years old who participated in a 24-week, randomized, double-blind clinical trial (CompoSIT-R [comparison of sitagliptin with dapagliflozin in mild renal impairment]; NCT02532855) in T2D patients with mild renal insufficiency and on metformin ± a sulfonylurea; the primary efficacy end point was change in HbA1c at week 24.

Results: Treatment groups were well balanced at baseline (mean HbA1c = 7.7/7.7% and eGFR = 79/76 ml/min/1.73 m^2 for sitagliptin/dapagliflozin). At week 24, LS mean (95% CI) change in HbA1c and percentage of patients with HbA1c < 7% were greater with sitagliptin, − 0.48% and 41%, respectively, compared with dapagliflozin, − 0.36% and 28%; between-group differences = − 0.12% (− 0.36, 0.01) and 12.8% (3.3, 22.2) for change in HbA1c and percentage with HbA1c < 7%, respectively. The sitagliptin group had greater reductions in PPG end points, while the dapagliflozin group had greater reductions in FPG. Treatments were generally well tolerated. There were fewer drug-related adverse events (AEs) with sitagliptin than with dapagliflozin but AE profiles were otherwise similar.

Conclusions: In patients ≥ 65 years of age with T2D and mild renal insufficiency with inadequate glycemic control on metformin ± sulfonylurea, treatment with sitagliptin for 24 weeks resulted in improvement in HbA1c relative to treatment with dapagliflozin that is consistent with that previously observed in the overall population. Both treatments were generally well tolerated.

Keywords: DPP-4; Elderly; Incretins; SGLT2

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A. Raji (✉) · Z. J. Xu · R. L. H. Lam · E. A. O'Neill · K. D. Kaufman · S. S. Engel
Merck & Co., Inc., Kenilworth, NJ, USA
e-mail: annaswamy.raji@merck.com

Key Summary Points

Why carry out this study?

The anti-hyperglycemic efficacy of sodium-glucose co-transporter 2 (SGLT2) inhibitors is dependent on kidney function.

Chronic kidney disease is prevalent in older patients with type 2 diabetes (T2D).

A recent clinical study comparing the efficacy and safety of the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin with the SGLT2 inhibitor dapagliflozin, in patients with T2D and mild renal insufficiency, provided data for a post hoc analysis of the effects of these treatments in participants ≥ 65 years of age.

What was learned from the study?

Treatment of patients ≥ 65 years of age with sitagliptin for 24 weeks resulted in improvement in HbA1c relative to treatment with dapagliflozin, a result consistent with that observed in the overall population in the primary study.

Both treatments were generally well tolerated by patients ≥ 65 years of age.

INTRODUCTION

Type 2 diabetes mellitus (T2D) prevalence is expected to increase from 9.3% of the global population of adults in 2019 to 10.2% by 2030 [1], and the number of people ≥ 65 years of age with T2D has been predicted to increase from nearly 136 million in 2019 to over 195 million by 2030 [1].

Older patients with T2D require particular care in the choice of antihyperglycemic agents (AHAs) due to age-associated comorbidities and complications such as increased risks of cardiovascular and renal diseases [2, 3] and hypoglycemic events [3, 4]. Chronic kidney disease (CKD) is a common complication of T2D, with an increased prevalence among patients ≥ 65 years of age, among whom 43% have moderate (stage 3, estimated glomerular filtration rate [eGFR] = ≥ 30 to < 60 ml/min/1.73 m^2) or severe (stage 4, eGFR ≥ 15 to < 30 ml/min/1.73 m^2) renal insufficiency and 48% have mild (stage 2, eGFR ≥ 60 to < 90 ml/min/1.73 m^2) renal insufficiency [5]. While it is generally recognized that renal function should be considered when choosing an AHA for treatment of T2D, often only CKD stages 3–5 are considered relevant to that decision [6]. This may be due, in part, to the fact that the influence of mild renal insufficiency on the efficacy and safety of most AHAs has not often been prospectively assessed in clinical trials.

Dipeptidyl peptidase 4 (DPP-4) inhibitors are both efficacious and well tolerated throughout the spectrum of renal function, although dose adjustment to regulate drug exposure may be required [7]. In contrast, the sodium-glucose co-transporter 2 (SGLT2) inhibitors have reduced glycemic efficacy in patients with moderate to severe renal insufficiency because of their mechanism of action [8].

In a recent prospective, randomized clinical trial, the DPP-4 inhibitor sitagliptin had greater glycemic efficacy compared with the SGLT2 inhibitor dapagliflozin in patients with T2D, mild renal insufficiency and inadequate glycemic control on metformin ± a sulfonylurea [9]. As nearly 70% of the patients in this study were ≥ 65 years old, the effects of these treatments on this population could be evaluated post hoc with a statistically robust data set.

An analysis of the data set was carried out to evaluate the antihyperglycemic efficacy and safety of sitagliptin compared with dapagliflozin. The results of the analysis are presented here.

METHODS

Data Source

Details of the primary study have been published. Briefly, it was a multinational, randomized, double-blind, active comparator-

controlled, parallel-group, non-inferiority study (MK-0431-838; CompoSIT-R [comparison of sitagliptin with dapagliflozin in mild renal impairment]; ClinicalTrials.gov identifier: NCT02532855; EudraCT: 2014-005525-13) comparing the efficacy and safety of sitagliptin to dapagliflozin when added on to metformin, alone or in combination with a sulfonylurea, in people with T2D and mild renal impairment (eGFR $\geq$ 60 and $<$ 90 ml/min/1.73 m^2) [9].

In the primary study, eligible patients (N = 614) were $\geq$ 25 years of age. Of these, n = 410 were $\geq$ 65 years of age and included in this post hoc analysis. All patients randomized in the primary study were on a stable dose of metformin ($\geq$ 1500 mg/day) alone or in combination with a sulfonylurea (SU) (at a dose of $\geq$ 50% of the maximum labeled dose in the country of the investigational site) for $\geq$ 8 weeks. Treatment groups were sitagliptin 100 mg/day or dapagliflozin initiated at 5 mg and titrated up to 10 mg at week 4. If, in the opinion of the investigator, a patient was unable to tolerate up-titration to 10 mg dapagliflozin, the dose was to remain at 5 mg.

All patients provided written informed consent to participate, and the study protocol was reviewed and approved by the appropriate committee and authority. The study was performed in accordance with the Declaration of Helsinki.

Analysis Endpoints

The efficacy endpoints presented here are changes from baseline in HbA1c, 2-h incremental post-prandial glucose excursion (PPGE), 2-h post-prandial glucose (PPG), fasting plasma glucose (FPG) and body weight, and the proportion of patients who achieved an HbA1c goal of $<$ 7% at week 24.

Safety endpoints presented are incidences of adverse events (AEs) overall and incidences of AEs of hypoglycemia, genital mycotic infection (GMI) and urinary tract infection (UTI). Safety data were collected until 2 weeks after discontinuation of treatment except for subjects who discontinued study medication prematurely, for whom safety data were collected until week 24.

Statistical Analysis

The analysis population consisted of all randomized patients $\geq$ 65 years of age who received at least one dose of study treatment. For efficacy analysis, inclusion required a baseline or post-randomization measurement for the relevant parameter.

To assess change from baseline in efficacy endpoints, a longitudinal data analysis (LDA) model including terms for treatment, time, background AHA (metformin alone or metformin in combination with a sulfonylurea), interaction of time by background AHA, and interaction of time by treatment, with a constraint that the true mean at baseline is common to all treatment groups, was used. The efficacy of sitagliptin compared with dapagliflozin was assessed using the estimated between-treatment difference from the LDA model. Analysis of percentage of individuals at the HbA1c goal of $<$ 7.0% at week 24 was based on estimated rates and confidence intervals for between-group rate differences computed using the Miettinen and Nurminen method [10]. For this analysis, multiple imputations of missing data, using techniques proposed by Rubin [11], were based on the LDA model used for analysis of HbA1c. Observed data were not imputed. Patients were categorized as being at the HbA1c goal or not at the goal at week 24 after imputations.

Safety analysis included a summary of all AEs as well as AEs of hypoglycemia, GMIs and UTIs.

RESULTS

Baseline demographic and anthropometric characteristics of the 410 patients $\geq$ 65 years of age in this analysis (n = 210 treated with sitagliptin and n = 200 treated with dapagliflozin) were generally similar (mean ages = 72.2/71.6 years, HbA1c = 7.7/7.7%, eGFR = 79.2/76.4 ml/min/1.73 m^2 in the sitagliptin/dapagliflozin groups; Table 1), although there were approximately 20% fewer female patients

Table 1 Baseline demographic, anthropometric and disease characteristics of analysis treatment groups

	Sitagliptin (*N* = 210)	**Dapagliflozin (*N* = 200)**
Age (years)	72.2 ± 5.1	71.6 ± 4.5
Female [*n* (%)]	100 (47.6)	81 (40.5)
Race [*n* (%)]		
White	161 (76.7)	155 (77.5)
Multiple	25 (11.9)	22 (11.0)
American Indian/Alaska Native	13 (6.2)	12 (6.0)
Asian	6 (2.9)	3 (1.5)
Black or African American	5 (2.4)	7 (3.5)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.5)
Ethnicity [*n* (%)]		
Not Hispanic or Latino	128 (61.0)	120 (60.0)
Hispanic or Latino	80 (38.1)	80 (40.0)
Not reported	2 (1.0)	0 (0.0)
Body weight (kg)	83.3 ± 17.2	85.2 ± 16.3
BMI (kg/m^2)	31.0 ± 5.1	30.7 ± 4.8
HbA1c (%)	7.7 ± 0.7	7.7 ± 0.8
FPG[a] (mg/dl)	163.2 ± 43.6	165.0 ± 40.5
eGFR (ml/min/1.73 m^2)	79.2 ± 10.7	76.4 ± 12.2
Duration of type 2 diabetes (years)	11.4 ± 7.5	12.1 ± 8.0
Background medication [*n* (%)]		
Metformin alone	150 (71.4)	149 (74.5)
Metformin + SU	60 (28.6)	51 (25.5)

Values are mean ± standard deviation unless otherwise noted
BMI body mass index, *FPG* fasting plasma glucose, *SU* sulfonylurea
[a] To convert to mmol/l divide mg/dl value by 18

in the dapagliflozin group compared with the sitagliptin group (dapagliflozin $n = 81$, sitagliptin $n = 100$).

After 24 weeks of treatment, both study medications improved glycemic control (Table 2). Decrease from baseline in HbA1c was greater in the sitagliptin group compared with the dapagliflozin group. This difference was primarily due to the greater effect of sitagliptin in the subgroup of patients on a background treatment of metformin alone compared with the effect of dapagliflozin in this subgroup (Table 2). Decrease from baseline in FPG was greater with dapagliflozin (Table 2). A greater percentage of patients were at HbA1c goal of < 7.0% after 24 weeks of treatment with sitagliptin (41.1%) compared with dapagliflozin

Table 2 Efficacy measures at week 24

Parameter	Sitagliptin	Dapagliflozin
HbA1c (%)		
Overall	(N = 210)	(N = 200)
Baseline	7.7 ± 0.7	7.7 ± 0.8
Week 24	7.1 ± 0.7	7.3 ± 0.6
Change from baseline[a]	− 0.48 (− 0.59, − 0.37)	− 0.36 (− 0.47, − 0.25)
Change vs. dapagliflozin[b]	− 0.12 (− 0.26, 0.01)	––
On background of metformin	(n = 150)	(n = 149)
Baseline	7.8 ± 0.7	7.6 ± 0.7
Week 24	7.1 ± 0.7	7.2 ± 0.6
Change from baseline[a]	− 0.50 (− 0.62, − 0.39)	− 0.35 (− 0.46, − 0.23)
Change vs. dapagliflozin[b]	− 0.16 (− 0.31, − 0.00)	––
On background of metformin + SU	(n = 60)	(n = 51)
Baseline	7.7 ± 0.7	8.0 ± 0.9
Week 24	7.1 ± 0.8	7.4 ± 0.6
Change from baseline[a]	− 0.40 (− 0.61, − 0.18)	− 0.45 (− 0.69, − 0.22)
Change vs. dapagliflozin[b]	0.06 (− 0.25, 0.37)	––
Glucose (mg/dl)		
2-h incremental PPGE[c] (mg/dl)	(n = 202)	(n = 191)
Baseline	101.3 ± 57.9	95.7 ± 48.8
Week 24	74.2 ± 51.1	78.0 ± 46.5
Change from baseline[a]	− 28.6 (− 36.1, − 21.0)	− 21.8 (− 29.5, − 14.0)
Change vs. dapagliflozin[b]	− 6.8 (− 15.9, 2.2)	––
2-h PPG[c] (mg/dl)	(n = 178)	(n = 167)
Baseline	264.0 ± 70.4	257.6 ± 65.2
Week 24	219.7 ± 58.4	219.2 ± 53.8
Change from baseline[a]	− 40.8 (− 48.5, − 33.2)	− 38.6 (− 46.5, − 30.7)
Change vs. dapagliflozin[b]	− 2.3 (− 12.5, 8.0)	––
FPG[c] (mg/dl)	(n = 210)	(n = 200)
Baseline	163.2 ± 43.6	165.0 ± 40.5
Week 24	144.1 ± 34.0	139.3 ± 27.6
Change from baseline[a]	− 16.2 (− 21.1, − 11.2)	− 22.7 (− 27.9, − 17.5)

Table 2 continued

Parameter	Sitagliptin	Dapagliflozin
Change vs. dapagliflozin[b]	6.5 (0.7, 12.3)	––

Values are mean ± standard deviation unless otherwise noted
PPGE post-prandial glucose excursion, *PPG* post-prandial glucose, *FPG* fasting plasma glucose
[a] Least squares (LS) mean (95% CI)
[b] Difference in LS means (95% CI)
[c] To convert to mmol/l divide mg/dl value by 18

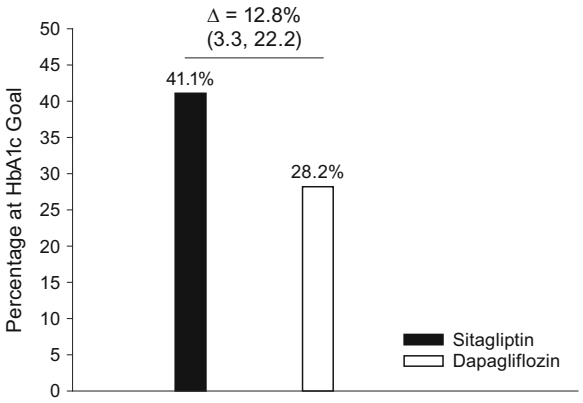

Fig. 1 Percentage of patients at goal of HbA1c < 7% at week 24, estimated from the LDA model described in Methods using standard multiple imputation techniques

(28.2%); the between-group difference (95% CI) was 12.8% (3.3, 22.2) (Fig. 1).

The LS mean (95% CI) change from baseline in body weight was greater in the dapagliflozin group compared with the sitagliptin group. The between-group difference was 1.96 kg (1.44, 2.48) (Table 3).

Except for drug-related AEs, the summary AE profiles of the two treatment arms were similar (Table 4). The greater incidence of drug-related AEs in the dapagliflozin arm was primarily driven by a greater incidence of GMIs and AEs associated with increased urine flow. There were no deaths in this study.

The overall incidence of AEs of hypoglycemia were similar in the two study arms, and greater in patients on a background medication of metformin and a sulfonylurea compared with those only on metformin (Table 4).

DISCUSSION

Sitagliptin and dapagliflozin represent two distinct classes of oral AHAs used for treatment of patients with T2D. Previous reports have addressed the safety and/or efficacy of one or the other in older patients (e.g., [12–16]), but none have evaluated these treatments in a population of older people with mild renal insufficiency. In this post hoc analysis of data from a previously reported primary study (CompoSIT-R [9]), the anti-hyperglycemic efficacy and safety of sitagliptin were compared to dapagliflozin in patients ≥ 65 years of age with

Table 3 LS mean (95% CI) changes from baseline body weight (kg) at week 24

	Sitagliptin (*N* = 193)	Dapagliflozin (*N* = 178)
Baseline	83.5 ± 17.4	85.2 ± 16.1
Week 24	83.2 ± 17.1	82.9 ± 16.1
Change from baseline[a]	− 0.29 (− 0.67, 0.08)	− 2.25 (− 2.65, − 1.85)
Change vs. dapagliflozin[b]	1.96 (1.44, 2.48)	––

Values are mean ± standard deviation unless otherwise noted
[a] Least squares (LS) mean (95% CI)
[b] Difference in LS means (95% CI)

Table 4 Adverse events (AEs) summary and specific AEs of interest

Patients [*n* (%)]	Sitagliptin (*N* = 210)	Dapagliflozin (*N* = 200)	Difference[a]
AE summary			
With one or more			
AEs	102 (48.6)	103 (51.5)	− 2.9 (− 12.5, 6.7)
Drug-related[b] AEs	16 (7.6)	30 (15.0)	− 7.4 (− 13.8, − 1.3)
Serious AEs	10 (4.8)	11 (5.5)	− 0.7 (− 5.4, 3.8)
Serious drug-related[b] AEs	0 (0.0)	0 (0.0)	0.0
Who died	0 (0.0)	0 (0.0)	0.0
Who discontinued due to			
An AE	8 (3.8)	4 (2.0)	1.8 (− 1.7, 5.6)
A drug-related[b] AE	3 (1.4)	2 (1.0)	0.4
A serious AE	3 (1.4)	1 (0.5)	0.9
A serious drug-related[b] AE	0 (0.0)	0 (0.0)	0.0
Hypoglycemia summary			
On metformin alone	(*n* = 150)	(*n* = 149)	
With one or more AE of hypoglycemia	4 (2.7)	6 (4.0)	− 1.4 (− 6.2, 3.2)
Symptomatic[c]	3 (2.0)	6 (4.0)	− 2.0 (− 6.8, 2.2)
Documented[d]	3 (2.0)	6 (4.0)	− 2.0 (− 6.8, 2.2)
Severe[e]	0 (0.0)	1 (0.7)	− 0.7
Asymptomatic[f]	1 (0.7)	1 (0.7)	0.0
On metformin and a sulfonylurea	(*n* = 60)	(*n* = 51)	
With one or more AE of hypoglycemia	9 (15.0)	6 (11.8)	3.2 (− 10.4, 16.3)
Symptomatic[c]	8 (13.3)	3 (5.9)	7.5 (− 4.4, 19.3)
Documented[d]	8 (13.3)	3 (5.9)	7.5 (− 4.4, 19.3)
Severe[e]	0 (0.0)	0 (0.0)	0.0
Asymptomatic[f]	4 (6.7)	3 (5.9)	0.8 (− 10.2, 11.0)
Genital mycotic infection (GMI)			
Female	(*n* = 100)	(*n* = 81)	
With one or more AE of GMI	0 (0.0)	4 (4.9)	–
Genital candidiasis	0 (0.0)	2 (2.5)	–
Genital infection fungal	0 (0.0)	1 (1.2)	–
Vulvovaginal mycotic infection	0 (0.0)	1 (1.2)	–
Male	(*n* = 110)	(*n* = 119)	
With one or more AE of GMI	1 (0.9)	4 (3.4)	–

Table 4 continued

Patients [*n* (%)]	Sitagliptin (*N* = 210)	Dapagliflozin (*N* = 200)	Difference[a]
Balanitis candida	1 (0.9)	3 (2.5)	–
Genital candidiasis	0 (0.0)	1 (0.8)	–
Urinary tract infection	2 (1.0)	5 (2.5)	–

[a] Difference in percentages. The 95% CI was computed only for those endpoints with at least four subjects having events in one or more treatment groups

[b] Assessed by the investigator as related to study drug

[c] Symptomatic hypoglycemia: episode with clinical symptoms attributed to hypoglycemia, without regard to glucose level

[d] Documented symptomatic hypoglycemia: episode with clinical symptoms attributed to hypoglycemia with a documented glucose level of $\leq$ 70 mg/dl

[e] Severe hypoglycemia: episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness or seizure were classified as having required medical assistance, whether or not medical assistance was obtained

[f] Asymptomatic hypoglycemia: finger-stick glucose values $\leq$ 70 mg/dl without symptoms

T2D and mild renal impairment. Sitagliptin treatment was associated with greater reduction from baseline in LS mean HbA1c and higher percentage of patients with HbA1C < 7.0% compared with dapagliflozin. Dapagliflozin treatment was associated with a greater reduction from baseline in LS mean FPG and a greater reduction in body weight compared with sitagliptin. Both treatments were generally well tolerated, with similar incidences of hypoglycemia in the two groups. There was a higher incidence of drug-related AEs in the dapagliflozin arm, primarily related to GMIs and increased urine flow.

A strength of this analysis is the large number of patients $\geq$ 65 years old available from the primary study. A limitation of the analysis is its post hoc nature. In addition, the results are relevant to the population studied and not necessarily to patients at other stages of CKD. Furthermore, the study evaluated sitagliptin and dapagliflozin, and results cannot be extrapolated to other DPP-4 or SGLT2 inhibitors.

CONCLUSIONS

In patients $\geq$ 65 years of age with T2D and mild renal insufficiency with inadequate glycemic control on metformin ± sulfonylurea, treatment with sitagliptin for 24 weeks resulted in an improvement in HbA1c relative to treatment with dapagliflozin that is consistent with that observed in the overall population [9]. Both treatments were generally well tolerated.

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Compliance with Ethics Guidelines. All patients provided written informed consent to participate, and the study protocol was reviewed and approved by the appropriate committee and authority. The study was performed in accordance with the Declaration of Helsinki.

Data Availability. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

REFERENCES

1. International Diabetes Federation Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation. 2019.
2. Abaterusso C, Lupo A, Ortalda V, De Biase V, Pani A, Muggeo M, et al. Treating elderly people with diabetes and stages 3 and 4 chronic kidney disease. Clin J Am Soc Nephrol. 2008;3(4):1185–94.
3. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults. Diabetes Care. 2012;35(12):2650–64.
4. Sinclair A, Bode B, Harris S, Vijapurkar U, Mayer C, Fung A, et al. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. BMC Endocr Disord. 2014;14:37.
5. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: improving Global Outcomes (KDIGO) staging. BMC Res Notes. 2014;7:415.
6. Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with chronic kidney disease. Clin Diabetes Endocrinol. 2015;1:2.
7. Deacon CF. A review of dipeptidyl peptidase-4 inhibitors. Hot topics from randomized controlled trials. Diabetes Obes Metab. 2018;20(Suppl 1):34–46.
8. Arnouts P, Bolignano D, Nistor I, Bilo H, Gnudi L, Heaf J, et al. Glucose-lowering drugs in patients with chronic kidney disease: a narrative review on pharmacokinetic properties. Nephrol Dial Transpl. 2014;29(7):1284–300.
9. Scott R, Morgan J, Zimmer Z, Lam RLH, O'Neill EA, Kaufman KD, et al. A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: the CompoSIT-R study. Diabetes Obes Metab. 2018;20(12):2876–84.
10. Miettinen O, Nurminen M. Comparative analysis of two rates. StatMed. 1985;4(2):213–26.
11. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
12. Round EM, Engel SS, Golm GT, Davies MJ, Kaufman KD, Goldstein BJ. Safety of sitagliptin in elderly patients with type 2 diabetes: a pooled analysis of 25 clinical studies. Drugs Aging. 2014;31(3):203–14.
13. Bethel MA, Engel SS, Green JB, Huang Z, Josse RG, Kaufman KD, et al. Assessing the safety of sitagliptin in older participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Care. 2017;40(4):494–501.
14. Shankar RR, Xu L, Golm GT, O'Neill EA, Goldstein BJ, Kaufman KD, et al. A comparison of glycaemic

effects of sitagliptin and sulfonylureas in elderly patients with type 2 diabetes mellitus. Int J Clin Pract. 2015;69(6):626–31.

15. Cahn A, Mosenzon O, Wiviott SD, Rozenberg A, Yanuv I, Goodrich EL, et al. Efficacy and safety of dapagliflozin in the elderly: analysis from the DECLARE-TIMI 58 Study. Diabetes Care. 2020;43(2):468–75.

16. Fioretto P, Mansfield TA, Ptaszynska A, Yavin Y, Johnsson E, Parikh S. Long-term safety of dapagliflozin in older patients with type 2 diabetes mellitus: a pooled analysis of phase IIb/III studies. Drugs Aging. 2016;33(7):511–22.