International Journal of Diabetes in Developing Countries
https://doi.org/10.1007/s13410-024-01337-1

EDITORIAL

Assessing glycemic and weight-lowering potential of oral semaglutide in type 2 diabetes compared to other GLP-1 receptor agonists in Indian context

Awadhesh Kumar Singh[1,2,3] · **Rajeev Chawla**[4]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown a significant reduction in glycated hemoglobin (HbA1c) and body weight in people with type 2 diabetes (T2D). In addition, some of the injectable GLP-1RAs such as liraglutide, semaglutide, and dulaglutide have shown a significant reduction in major adverse cardiovascular events (MACE). Among the injected GLP-1RAs, semaglutide deserves special mention at least for two reasons. A higher strength of injectable semaglutide (2.4 mg) is also approved for obesity. Secondly, injectable semaglutide (1.0 mg) has shown superior HbA1C and weight lowering in T2D over several active comparators in the Phase 3 Clinical Development Programme named SUSTAIN (Semaglutide Unabated Sustainability In Treatment of Type 2 Diabetes). This includes the superiority of injectable semaglutide 1.0 mg in both HbA1c and weight lowering over sitagliptin 100 mg (SUSTAIN 2, Global), canagliflozin 300 mg (SUSTAIN 8, Global), liraglutide 1.2 mg (SUSTAIN 10, European), dulaglutide 1.5 mg (SUSTAIN 7, Global), exenatide extended-release 2.0 (SUSTAIN 3, Global), and basal insulin glargine (SUSTAIN 4, Global) [1–6]. However, injectable semaglutide is not yet available in India. Currently, only two injectable GLP-1RAs such as liraglutide and dulaglutide are available in India. Among these two GLP-1RAs, liraglutide has shown a small but significantly higher weight loss compared to dulaglutide despite similar HbA1c control in AWARD 6 (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes-6) [7].

Orally administered semaglutide is the first oral GLP-1RA approved in 2020 by the United States (US) Food and Drug Administration, the European Medicines Agency, and the Drug Controller General of India (DCGI) for the treatment of T2D, based on extensive Phase 3 Clinical Development Programme named PIONEER (Peptide InnOvatioN for Early diabEtes tReatment). Interestingly, like injectable semaglutide (1.0 mg), oral semaglutide (14 mg) daily has also shown superior HbA1c and weight lowering compared to several active comparators that include empagliflozin 25 mg (PIONEER 2, Global), sitagliptin 100 mg (PIONEER 3 and PIONEER 7, Global), injectable liraglutide 0.9 mg (PIONEER 9, Japanese) and 1.8 mg (PIONEER 4, Global), and injectable dulaglutide 0.75 mg (PIONEER 10, Japanese) [8–13]. These findings suggest that both formulations of semaglutide are seemingly effective HbA1c and weight-lowering agents in people with T2D. Interestingly, there are no Phase 3 head-to-head randomized controlled trials (RCTs) that compared these two formulations of semaglutide in people with T2D. However, an indirect comparison of PIONEER 1 and SUSTAIN 1 trial with oral *vs.* injectable semaglutide, respectively, (against placebo) showed similar proportions of patients with T2D achieved ≥ 5% (44% *vs.* 45%, respectively) and ≥ 10% (14% *vs.* 13%) weight loss despite a higher baseline mean body weight in SUSTAIN 1 (96.8 kg) compared with PIONEER 1 (88.1 kg) [14]. These observations concur with the findings from a study that showed a similar circulating level of semaglutide exposure with two different formulations of oral (14 mg) *vs.* injectable semaglutide (1.0 mg) [15].

Recently, a few observational studies have compared the safety and efficacy of oral *vs.* injectable semaglutide in people with T2D. A retrospective, single-center study (n = 103) from the UK [16] studied the comparative effectiveness of oral (n = 53) *vs.* injectable semaglutide (n =

✉ Awadhesh Kumar Singh
drawadheshkumarsingh@gmail.com

1 G. D Hospital & Diabetes Institute, Kolkata 700013, West Bengal, India

2 Horizon Multispeciality Hospital, Kolkata, West Bengal, India

3 Sun Valley Hospital & Diabetes Research Centre, Guwahati, Assam, India

4 North Delhi Diabetes Centre, Rohini, New Delhi, India

Published online: 17 April 2024

Table 1 Head-to-head randomized controlled trials of GLP-1RAs in people with type 2 diabetes

Trial eponym	Comparator arms, *N*	Duration (weeks)	Mean HbA1c (%) changes at EOS	Δ HbA1c (%) at EOS, *p*-value	Mean weight (kg) changes at EOS	Δ Weight (kg) at EOS, *p*-value	Adverse events	Drug discontinuation due to any cause
PIONEER 4 [12]	SEMA 14, 285	52	−1.2	−0.3, $p = 0.0002$	−4.3	−1.3, $p = 0.002$	Nausea: 20%	11%
	LIRA 1.8, 284		−0.9		−3.0		Nausea: 18%	9%
PIONEER 9 [11]	SEMA 14, 48	52	−1.5	−0.3, $p = 0.1$	−2.6	−2.7, $p < 0.0001$	Nausea: 8%	4%
	LIRA 0.9, 48		−1.2		0		Nausea: 0%	0%
PIONEER 10 [13]	SEMA 14, 130	52	−1.7	−0.3, $p = 0.02$	−1.6	−2.6, $p < 0.0001$	Nausea: 9%	6%
	DULA 0.75, 65		−1.4		+1.0		Nausea: 9%	3%
AWARD 6 [7]	DULA 1.5, 299	26	−1.42	−0.06, $p > 0.05$	−2.90	0.71, $p = 0.01$	GI: 36%	6%
	LIRA 1.8, 300		−1.36		−3.61		GI: 36%	6%
SUSTAIN 3 [5]	SEMA 1.0, 404	56	−1.5	−0.62, $p < 0.0001$	−5.6	−3.78, $p < 0.0001$	Nausea: 22%	9%
	EXE ER 2.0, 405		−0.9		−1.9		Nausea: 12%	7%
SUSTAIN 7 [4]	SEMA 1.0, 300	40	−1.8	−0.41, $p < 0.0001$	−6.5	−3.55, $p < 0.0001$	GI: 44%	10%
	DULA 1.5, 299		−1.4		−3.0		GI: 48%	7%
SUSTAIN 10 [3]	SEMA 1.0, 290	30	−1.7	−0.69, $p < 0.0001$	−5.8	−3.83, $p < 0.0001$	GI: 44%	11%
	LIRA 1.2, 287		−1.0		−1.9		GI: 38%	7%

PIONEER Peptide InnOvatioN for Early diabEtes tReatment, *AWARD* Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes, *SUSTAIN*, Semaglutide Unabated Sustainability In Treatment of Type 2 Diabetes, *HbA1c* glycated hemoglobin, *EOS* end of study, *GI* gastrointestinal, *SEMA* semaglutide, *LIRA* liraglutide, *DULA* dulaglutide, *EXE ER* exenatide extended-release

50) in T2D. There was no significant difference in mean HbA1c (−1.77% *vs.* −1.90%), mean body weight (−9.0 kg *vs.* −7.2 kg), and mean body mass index (BMI −3.3 kg/m^2 *vs.* −2.5 kg/m^2) lowering with oral *vs.* injectable semaglutide, respectively, at 6-month (p = not significant, for all parameters). Concerning adverse events, gastrointestinal (GI) side effects were similar with both formulations (47% *vs.* 52% with oral *vs.* injectable semaglutide, respectively), and 17% of oral and 10% of injectable semaglutide receivers discontinued the treatment for various reasons. Another

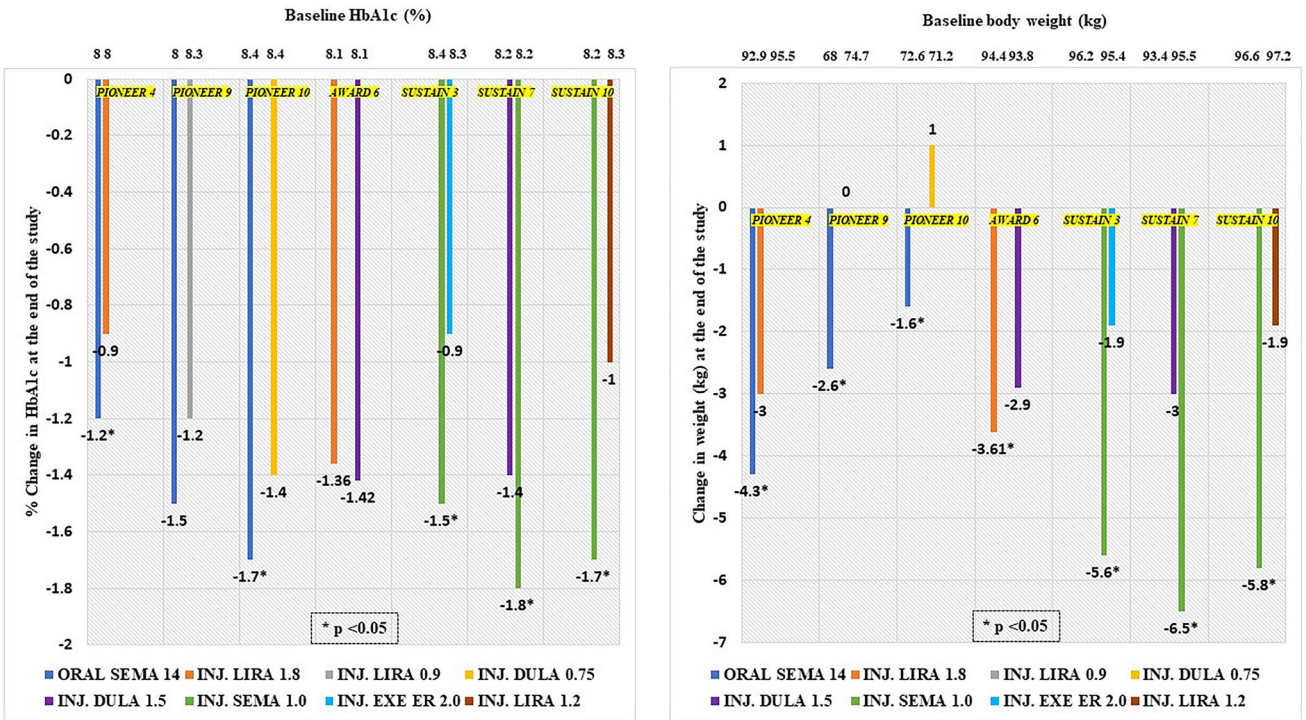

Fig. 1 HbA1c and body weight lowering with GLP-1RAs (head-to-head) in people with type 2 diabetes in RCTs

Table 2 Comparative retrospective studies with oral vs. injectable semaglutide in type 2 diabetes

First author, country	Drug arm, *n*	Duration of study	Male (%)	Mean age, (Yrs.)	Mean weight, (Kg)	Mean BMI (Kg/m^2)	Mean HbA1c (%)	eCVD (%)	Mean HbA1c changes at EOS (%)	Mean weight changes at EOS, (kg)	A1c < 6.5% achieved	≥ 5% weight loss	≥ 10% weight loss	Adverse events	Drug discontinued
Chowdhury et al. [16], UK	Oral, *n* = 53	6 M	49	58.5	109.7	39.3	9.28	11	−1.77	−9.0	NR	NR	NR	GI: 47%.	17%
	Inj., *n* = 50		46	56	114.0	40.0	9.48	14	−1.90	−7.2	NR	NR	NR	GI: 52%	10%
Fadini et al. [18], Italy	Oral, *n* = 107*	18 M	63.6	64.5	83.3	29.3	7.8	14	−0.9	−3.3	34.6	36 %	NR	NR	60% Continued
	Inj., *n* = 107*		63.6	64	84.6	29.7	7.7	10.8	−0.9	−3.7	34.6	52.1 %	NR	NR	70% Continued
Klobucar et al. [17], Croatia	Oral, *n* = 53	6 M	56.6	59!	97.3!	32.9!	8.8!	17	−1.40!	−5.9!	NR	NR	15.1 %	Nausea: 20%	0%
	Inj., *n* = 53		56.6	63!	102!	34.7!	8.0!	22.6	−1.10!	−6.5!	NR	NR	20.7%	Nausea: 22%	0%

Yrs years, *M* months, *Inj.* injectable, *UK* United Kingdom, *BMI* body mass index, *eCVD* established cardiovascular disease, *EOS* end of the study, *Kg* kilograms, *GI* gastrointestinal, *NR* not reported/ retrievable

*Propensity-matched

!Median values

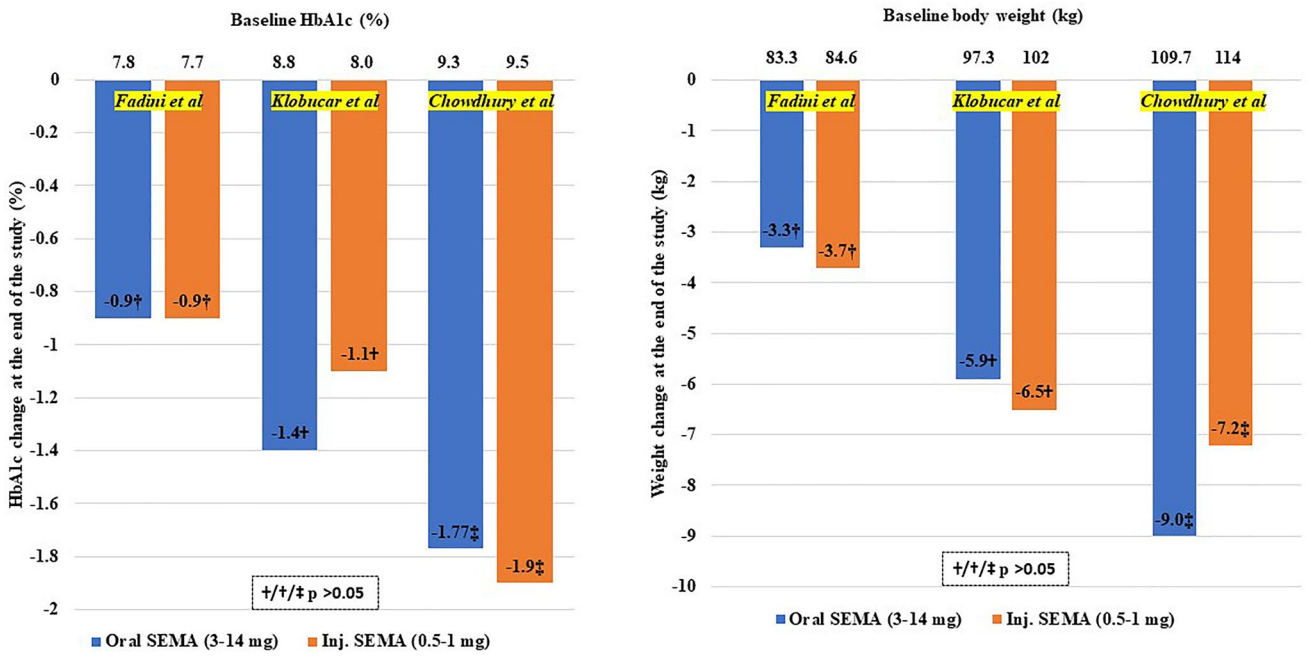

Fig. 2 HbA1c and body weight lowering with oral vs. injectable semaglutide in people with type 2 diabetes in real-world studies

single-center retrospective study ($n = 106$) from Croatia [17] compared the effectiveness of oral *vs.* injectable semaglutide in people with T2D, who are naïve to GLP-1RA. This study showed no significant difference in median HbA1c (−1.4% *vs.* −1.1%, $p = 0.13$) and median body weight (−5.9 kg *vs.* −6.5 kg, $p = 0.71$)) reduction between oral *vs.* injectable semaglutide, respectively, at 6 months. Notably, while baseline median HbA1c was significantly higher in the oral semaglutide arm (8.8% *vs.* 8.0%, oral *vs.* injectable semaglutide, respectively, $p = 0.04$), body weight was insignificantly higher in the injectable semaglutide arm (97.3 kg *vs.* 102 kg, oral *vs.* injectable semaglutide, respectively, $p = 0.08$). A weight loss of > 10% was achieved in similar proportions of patients with T2D on both formulations (15.1% *vs.* 20.7%, oral *vs.* injectable semaglutide, respectively, $p > 0.05$). Concerning safety, nausea, the most common GI side effect was seen in similar proportions of patients with both formulations (20% *vs.* 22%, oral *vs.* injectable semaglutide, respectively) and none discontinued the treatment in both arms. Similarly, a propensity-matched, retrospective study ($n = 214$) from Italy [18] comparatively assessed the effectiveness of oral ($n = 107$) *vs.* injectable ($n = 107$) semaglutide in people with T2D for 18 months. Both formulations of semaglutide reduced HbA1c (−0.9% in each arm) and body weight (−3.3 kg *vs.* −3.7 kg, oral *vs.* semaglutide, respectively) similarly at 18 months. However, a higher proportion of patients have ≥ 5% weight loss (52% *vs.* 36%) and persistently continued (70% *vs.* 60%) on injectable *vs.* oral semaglutide, respectively.

Collectively, the HbA1c and weight-lowering potential of oral semaglutide (7–14 mg) appear to be nearly similar to injectable semaglutide (0.5–1.0 mg) and larger than other GLP-1RAs, currently approved in people with T2D. Table 1 summarizes the findings of results from the head-to-head RCTs of GLP-1RAs conducted to date and Figure 1 graphically represents the efficacy outcome. Table 2 summarizes the baseline characteristics and findings of results from the observational studies conducted to date that compared oral *vs.* injectable semaglutide, and Figure 2 graphically represents the efficacy outcome. Notwithstanding, unlike injectable semaglutide which has shown a significant reduction in MACE (SUSTAIN 6) and has an additional label for cardiovascular (CV) risk reduction, oral semaglutide is yet to show CV superiority over placebo (PIONEER 6) [19, 20]. Since PIONEER 6 was not powered to assess the CV superiority of oral semaglutide over placebo, the SOUL (Semaglutide cardiOvascular oUtcomes triaL, NCT03914326) has been specifically designed for this purpose and is estimated to be complete by July 2024 [21].

Author contribution All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work.

References

1. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5:341–54.
2. Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7:834–44.
3. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020;46(2):100–9. https://doi.org/10.1016/j.diabet.2019.101117.
4. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6:275–86.
5. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41:258–66.
6. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:355–66.
7. Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384(9951):1349–57.
8. Rodbard HW, Rosenstock J, Canani LH, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019;42(12):2272–81.
9. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. JAMA. 2019;321(15):1466–80.
10. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):528–39.
11. Yamada Y, Katagiri H, Hamamoto Y, et al. Dose-response, efficacy and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, multicentre trial. Lancet Diabetes Endocrinol. 2020;8(5):377–91.
12. Pratley RE, Amod A, Tetens Hoff S, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double blind, phase 3a trial. Lancet. 2019;394(10192):39–50.
13. Yabe D, Nakamura J, Kaneto H, et al. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2020;8(5):392–406.
14. Singh AK. Gauging the antiobesity potential of oral semaglutide in type 2 diabetes in the Indian context. Indian Journal Of Clinical Practice. 2023;33(11):8–12.
15. Overgaard RV, Hertz CL, Ingwersen SH, Navarria A, Drucker DJ. Levels of circulating semaglutide determine reductions in HbA1c and body weight in people with type 2 diabetes. Cell Rep Med. 2021;2(9):100387.
16 Roy Chowdhury S, Sadouki F, Collins E, et al. Real-world use of oral and subcutaneous semaglutide in routine clinical practice in the UK: a single-centre, retrospective observational study. Diabetes Ther. 2024;15:869–81. https://doi.org/10.1007/s13300-024-01551-4.
17. Klobučar S, Belančić A, Bukša I, Morić N, Rahelić D. Effectiveness of oral versus injectable semaglutide in adults with type 2 diabetes: results from a retrospective observational study in Croatia. Diabetology. 2024;5:60–8. https://doi.org/10.3390/diabetology5010005.
18. Fadini GP, Bonora BM, Ghiani M, Anichini R, Melchionda E, Fattor B, Fazion S, Meregalli G, Giaccari A, Avogaro A, Consoli A; GLIMPLES study investigators. Oral or injectable semaglutide for the management of type 2 diabetes in routine care: a multicentre observational study comparing matched cohorts. Diabetes Obes Metab. 2024. https://doi.org/10.1111/dom.15554.
19. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T. SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44.
20. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841–51.
21. McGuire DK, Busui RP, Deanfield J, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: design and baseline characteristics of SOUL, a randomized trial. Diabetes Obes Metab. 2023;25(7):1932–41.