Dulaglutide is a once-weekly glucagon-like peptide-1 receptor agonist approved for the treatment of type 2 diabetes (T2D). Integrated data from 9 phase II and III trials in people with T2D (N = 6005) were used to evaluate the effects of dulaglutide on estimated glomerular filtration rate (eGFR [Chronic Kidney Disease Epidemiology Collaboration]), urine albumin-to-creatinine ratio (UACR) and kidney adverse events (AEs). No significant differences in eGFR were observed during treatment for dulaglutide vs placebo, active comparators or insulin glargine (mean ± standard deviation values: dulaglutide vs placebo: 87.8 ± 17.7 vs 88.2 ± 17.9 mL/min/1.73 m², P = .075; dulaglutide vs active comparators: 89.9 ± 16.7 vs 88.8 ± 16.3 mL/min/1.73 m², P = .223; and dulaglutide vs insulin glargine: 85.9 ± 18.2 vs 83.9 ± 18.6 mL/min/1.73 m², P = .423). Lower UACR values were observed for dulaglutide vs placebo, active comparators and insulin glargine (at 26 weeks, median [Q1-Q3] values were: dulaglutide vs placebo: 8.0 [4.4-20.4] vs 8.0 [4.4-23.9] mg/g, P = .023; dulaglutide vs active comparators: 8.0 [4.4-21.2] vs 8.9 [4.4-27.4] mg/g, P = .013; and dulaglutide vs insulin glargine: 8.9 [4.4-29.2] vs 12.4 [5.3-50.5] mg/g, P = .029). AEs reflecting potential acute renal failure were 3.4, 1.7 and 7.0 events/1000 patient-years for dulaglutide, active comparators and placebo, respectively. In conclusion, dulaglutide treatment of clinical trial participants with T2D did not affect eGFR and slightly decreased albuminuria.

**KEYWORDS**
clinical trial, diabetes complications, diabetic nephropathy, dulaglutide, GLP-1, type 2 diabetes

---

### INTRODUCTION

Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD) worldwide. Patients with T2D and low kidney function have limited treatment options because medications that are cleared by the kidney (e.g., biguanides and some sulphonylureas) often require dosage adjustments, and many are contraindicated. In addition, patients with T2D and CKD are at a higher risk of hypoglycaemia compared with patients with T2D because of decreased gluconeogenesis by the kidney as well as decreased clearance of insulin and of some other diabetes medications. Diabetes medications not cleared by the kidney and associated with a low risk of hypoglycaemia would represent a clinically significant advance for patients with T2D and CKD.

Dulaglutide is a once-weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA). In phase II and phase III registration studies, dulaglutide was found to have superior glycaemic efficacy compared with placebo, exenatide, insulin glargine, metformin and sitagliptin. Because of its large molecular size, dulaglutide is not cleared by the kidney, but is presumably catabolized by proteolytic degradation. In a phase I study, no clinically relevant change in the pharmacokinetics of dulaglutide was observed in participants with low kidney function. The primary objective of the present study was to evaluate the effects of dulaglutide on kidney function and safety in patients with T2D.

This study presents integrated data from 9 clinical trials (ClinicalTrials.gov): NCT00630825; NCT00791479; NCT01001104;
NCT01149421; NCT01064687; NCT00734474; NCT01075282; NCT01191268; and NCT01126580.

2 | RESEARCH DESIGN AND METHODS

Integrated individual-level data from 6 completed phase II and III registration studies which evaluated dulaglutide doses of 0.75 and 1.5 mg, with treatment duration of at least 26 weeks, were used to evaluate the effect of dulaglutide on kidney function (Table S1, Appendix S1). In 2 studies, AWARD-1 and AWARD-5, after 26 weeks, participants receiving placebo were switched to dulaglutide or sitagliptin, respectively. Data collected after the switch from placebo to active treatment were not included in the analyses of serum creatinine (sCr), estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR). The effects of dulaglutide on sCr, eGFR and UACR were compared with: (1) placebo at 26 weeks (AWARD-1, AWARD-5, and a phase II ambulatory blood pressure monitoring study); (2) all active comparators combined at 26, 52 and up to 104 weeks (AWARD-1, exenatide twice daily [1 study], insulin glargine [2 studies], metformin [1 study], and sitagliptin [1 study]); or (3) insulin glargine at 26 and 52 weeks (AWARD-2 and AWARD-4). Dulaglutide was compared with insulin glargine alone to avoid the confounding effects of similar drug classes in the active comparator group (exenatide in AWARD-1 and sitagliptin in AWARD-5).

Measurements of sCr, eGFR and UACR were performed by a central laboratory. eGFR was calculated using sCr and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. UACR was based on spot urine samples and was calculated as the ratio of urinary albumin (mg) to urinary creatinine (g).

Three additional placebo-controlled phase II studies, which did not evaluate both 0.75 and 1.5 mg dulaglutide doses (and were of short treatment durations), were only included for the purpose of identifying potential acute renal failure adverse events (AEs) throughout the dulaglutide clinical development programme. These studies were not included in the evaluation of kidney function because of the short treatment period and the lack of both dulaglutide doses.

Details of the statistical analyses are presented in Appendix S1.

3 | RESULTS

3.1 | Demographics and baseline characteristics

A total of 6005 study participants received the study drug in the 9 completed phase II and III registration studies. At baseline, across the 9 studies, 4.4% (n = 265) of participants had persistent eGFR <60 mL/min/1.73 m², 3% (n = 181) had persistent macroalbuminuria (defined as UACR >300 mg/g), and 7.1% (n = 425) had eGFR <60 mL/min/1.73 m² and/or macroalbuminuria. The 6 studies used to evaluate the effects of dulaglutide on kidney function included a broad range of patients with T2D whose diabetes duration ranged from 2.6 to 12.7 years (Table 1).

In the 3 placebo studies, proportions of participants who used antihypertensive medications, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were similar in the placebo arm and the dulaglutide arm (placebo 69.9%, 43.5% and 20.6%; dulaglutide 67.5%, 41.8% and 19.5%, respectively; P = .299). Across all 6 studies, 67.6% of participants receiving dulaglutide used antihypertensive medications with 39.4% using ACE inhibitors and 20.5% using ARBs.

3.2 | Effects of dulaglutide on sCr, eGFR and UACR

In the 3 placebo-controlled studies, baseline sCr, eGFR and UACR values for placebo and the all-dulaglutide (0.75 mg dose and 1.5 mg dose groups combined) group were similar (Table S2, Appendix S1). No significant difference was observed in sCr or eGFR between placebo and the all-dulaglutide group over 26 weeks of treatment (Figure 1A,D). In response to treatment with dulaglutide or placebo up to 26 weeks, UACR decreased slightly in both groups (Figure 1G). The decrease in UACR was slightly greater in the dulaglutide group compared with placebo (median percent change −16.7% vs −10.0%; P = .043 [Table S2, Appendix S1]).

In the 5 phase III studies that evaluated dulaglutide vs active comparator, baseline sCr and eGFR levels were comparable between the all-dulaglutide and active comparator groups (Table S2, Appendix S1). No significant difference was observed in sCr or eGFR between the 2 groups with treatment up to 104 weeks (Figure 1B,E). Baseline UACR was slightly higher in the active comparator group (Table S2, Appendix S1 and Figure 1H). In response to treatment with dulaglutide or active comparator up to 104 weeks, UACR tended to decrease in both groups (Figure 1H). UACR levels were slightly lower in the dulaglutide group compared with the active comparator group (Figure 1H). At 26 weeks, median percent changes were −20.0% vs −12.5%, respectively (Table S2, Appendix S1).

In the 2 phase III studies that evaluated dulaglutide vs insulin glargine, baseline sCr and eGFR levels were similar in the all-dulaglutide and insulin glargine groups (Table S2, Appendix S1). No significant difference was observed in sCr or eGFR between the 2 groups with treatment up to 52 weeks (Figure 1C,F). Baseline UACR was slightly higher in the insulin glargine group (Table S2, Appendix S1 and Figure 1I). UACR levels tended to be lower in the dulaglutide group compared with the insulin glargine group (Figure 1I). At 26 weeks, median percent changes in UACR from baseline were −20.0% for dulaglutide vs −9.4% for insulin glargine. At 52 weeks, the median percent decrease in UACR was −16.7% for dulaglutide and −3.7% for insulin glargine (Table S2, Appendix S1).

3.3 | Proportions of participants with 30% or 40% decline in eGFR

The number of participants who experienced a 30% or 40% decline in eGFR over time was not significantly different for dulaglutide-treated participants compared with placebo and all active comparators combined (Table S3, Appendix S1); however, in comparison with insulin glargine, there were significantly fewer dulaglutide-treated participants who experienced a 40% decline in eGFR at any point...
During a 1-year treatment period (0.26% vs 1.25%; \( P = .012 \) [Table S3, Appendix S1]).

### 3.4 AEs reflecting potential acute renal failure

In the 9 completed phase II and III studies, 4006 received dulaglutide (3531 patient-years), 703 received placebo (284 patient-years) and 1541 received active comparator (1722 patient-years). Some study participants received placebo followed by dulaglutide (n = 121) or sitagliptin (n = 124) and are included in the totals for each drug. \(^5\) AEs reflecting potential acute renal failure (Table S4, Appendix S1) were reported at rates of 3.4 (n = 12), 1.7 (n = 3) and 7.0 (n = 2) events per 1000 patient-years of exposure for dulaglutide, active comparators and placebo, respectively. Details regarding the 12 dulaglutide participants who reported an AE reflecting potential acute renal failure are included in Appendix S1.

### 4 DISCUSSION

Dulaglutide treatment in clinical trials for T2D did not affect eGFR, was associated with a slight decrease in albuminuria, and was not associated with an increase in AEs reflecting potential acute renal failure. Several studies have also shown that treatment of patients with T2D with other GLP-1 RAs did not alter sCr or eGFR;\(^7-9\) however, post-marketing cases of pre-renal acute decreases in kidney function have been reported with some GLP-1 RAs.\(^10-12\) This has been attributed to volume depletion that may occur in patients who experience excessive nausea, diarrhoea and vomiting.\(^10-12\) In patients with low kidney function, treatment with GLP-1 RAs that are cleared by the kidney may increase gastrointestinal AEs\(^13\) because of increased exposure to the medication. Consequently, the renally cleared GLP-1 RAs are not recommended to be used in patients with severely reduced kidney function.\(^14-16\) Elevated rates of gastrointestinal AEs in patients with low kidney function have also been reported with other GLP-1 RAs that are not cleared by the kidney;\(^7,17\) therefore, it is recommended to use these medications with caution when initiating or escalating doses in patients with renal impairment.\(^17,18\)

Dulaglutide exposure is not altered in patients with various degrees of reduced kidney function.\(^5\) Although long-term treatment with GLP-1 RAs did not alter eGFR in patients with T2D,\(^7-9\) controversy exists regarding acute effects of GLP-1 RAs on renal haemodynamics.\(^19-21\) The present data show that dulaglutide exposure is not altered in patients with various degrees of reduced kidney function.\(^5\) Although long-term treatment with GLP-1 RAs did not alter eGFR in patients with T2D,\(^7-9\) controversy exists regarding acute effects of GLP-1 RAs on renal haemodynamics.\(^19-21\) The present data show that dulaglutide

**TABLE 1 Summary of baseline demographics and renal characteristics in clinical trials of duration ≥26 weeks**

| Variable | AWARD-1 N = 976 | AWARD-2 N = 807 | AWARD-3 N = 807 | AWARD-4 N = 884 | AWARD-5 N = 1202 | ABPM study N = 755 |
|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------|
| Sex: female, n (%) | 406 (41.6) | 393 (48.7) | 454 (56.3) | 411 (46.5) | 643 (53.5) | 363 (48.1) |
| Mean (s.d.) age, years | 55.7 (9.8) | 56.7 (9.5) | 55.6 (10.4) | 59.4 (9.2) | 54.1 (9.9) | 56.5 (10.3) |
| Age <65 years, n (%) | 820 (84.0) | 646 (80.0) | 664 (82.3) | 641 (72.5) | 1048 (87.2) | 608 (80.5) |
| Ethnicity, n (%) | | | | | | |
| Not Hispanic or Latino | 644 (66.0) | 516 (63.9) | 535 (66.3) | 581 (65.7) | 950 (79.0) | 468 (62.0) |
| Hispanic or Latino | 331 (33.9) | 291 (36.1) | 272 (33.7) | 303 (34.3) | 251 (20.9) | 287 (38.0) |
| Unknown | 1 (.1) | 0 (0) | 0 (0) | 1 (.1) | 0 (0) | |
| Race, n (%) | | | | | | |
| White | 726 (74.4) | 570 (70.6) | 600 (74.3) | 697 (78.8) | 613 (51.0) | 608 (80.5) |
| Asian | 24 (2.5) | 137 (17.0) | 61 (7.6) | 35 (4.0) | 285 (23.7) | 69 (9.1) |
| American-Indian or Alaska Native | 135 (13.8) | 89 (11.0) | 85 (10.5) | 46 (5.2) | 1 (.1) | 2 (.3) |
| African-American | 76 (7.8) | 4 (5) | 53 (6.6) | 85 (9.6) | 50 (4.2) | 66 (8.7) |
| Multiple or unknown\(^5\) | 12 (1.2) | 7 (9) | 7 (9) | 20 (2.3) | 252 (21.0) | 9 (1.2) |
| Native Hawaiian or Other Pacific Islander | 3 (.3) | 0 (0) | 1 (.1) | 1 (.1) | 1 (.1) | 1 (.1) |
| Mean (s.d.) BMI, kg/m\(^2\) | 33.2 (5.4) | 31.6 (5.5) | 33.3 (5.5) | 32.5 (5.2) | 31.3 (4.4) | 33.0 (6.0) |
| Mean (s.d.) duration of diabetes, years | 8.8 (5.6) | 9.1 (6.0) | 2.6 (1.8) | 12.7 (7.0) | 7.1 (5.1) | 8.3 (5.9) |
| Mean (s.d.) HbA1c, % | 8.1 (1.3) | 8.1 (1.0) | 7.6 (0.9) | 8.5 (1.0) | 8.1 (1.1) | 7.9 (0.8) |
| UACR > 300 mg/g and/or eGFR <60 mL/min/1.73 m\(^2\), n (%)\(^4\) | 50 (5.1) | 37 (4.6) | 50 (6.2) | 132 (14.9) | 53 (4.4) | 69 (9.1) |
| Macroalbuminuria (UACR > 300 mg/g), n (%)\(^4\) | 23 (2.4) | 28 (3.5) | 20 (2.5) | 52 (5.9) | 30 (2.5) | 24 (3.2) |
| eGFR <60 mL/min/1.73 m\(^2\), n (%)\(^2,5\) | 27 (2.8) | 9 (1.1) | 30 (3.7) | 93 (10.5) | 25 (2.1) | 51 (6.8) |

Abbreviations: ABPM, ambulatory blood pressure monitoring; BMI, body mass index; s.d., standard deviation.

\(^1\) Multiple or Unknown includes patients self-declared as Hispanic race in AWARD-5.

\(^2\) eGFR was calculated based on the CKD-EPI equation\(^6\) and serum creatinine value, using the highest measured value of eGFR (CKD-EPI).

\(^3\) Patients were included if they met criteria for either the UACR > 300 mg/g or eGFR (CKD-EPI) <60 mL/min/1.73 m\(^2\) group as shown in Footnotes 4 and 5 below.

\(^4\) Patients were included if UACR >300 mg/g at all measured timepoints during baseline.

\(^5\) Patients were included if eGFR (CKD-EPI) <60 mL/min/1.73 m\(^2\) at all measured timepoints during baseline.

---

**TUTTLE ET AL.**
A small decrease in eGFR by 30% or 40% were generally similar for dulaglutide and placebo, active comparators or insulin glargine, except that proportion of patients experiencing a decline in eGFR by 40% was significantly lower with dulaglutide compared with insulin glargine. In the dulaglutide studies, there were very few patient reports of AEs potentially reflecting acute renal failure and the rate of patients in the dulaglutide groups who experienced these events was similar to the placebo and active comparator groups, taking into account the duration of treatment exposure. Only 2 events indicated typical acute renal failure; 1 attributable to sepsis and 1 to dehydration (Appendix S1). These AE data, together with the eGFR data, indicate that dulaglutide is not associated with an increased risk of acute renal failure.

A small decrease in UACR was observed in the dulaglutide group compared with placebo, all active comparators combined, or insulin glargine. A small decline in eGFR of 1 to 3 mL/min/1.73 m² was observed in all treatment groups (treatment duration 26-104 weeks), an expected finding based on normal ageing.22 eGFR typically declines even more, ~2 to 4 mL/min/y, in patients with T2D and diabetic kidney disease.22-24 In addition, proportions of patients experiencing a decline in eGFR by 30% or 40% were generally similar for dulaglutide and placebo, active comparators or insulin glargine, except that proportion of patients experiencing a decline in eGFR by 40% was significantly lower with dulaglutide compared with insulin glargine. In the dulaglutide studies, there were very few patient reports of AEs potentially reflecting acute renal failure and the rate of patients in the dulaglutide groups who experienced these events was similar to the placebo and active comparator groups, taking into account the duration of treatment exposure. Only 2 events indicated typical acute renal failure; 1 attributable to sepsis and 1 to dehydration (Appendix S1). These AE data, together with the eGFR data, indicate that dulaglutide is not associated with an increased risk of acute renal failure.

A small decrease in UACR was observed in the dulaglutide group compared with placebo, all active comparators combined, or insulin glargine, but the observed decrease was not of immediate clinical significance. Nevertheless, the dulaglutide albuminuria-lowering effect, similar to that of other GLP-1 RAs,25,26 suggests that treatment with dulaglutide could exert long-term renoprotective effects. Preclinical and early clinical data show that GLP-1 receptors are expressed in the kidney and provide rationale that GLP-1 RAs may exert...
renoprotective effects by decreasing albuminuria through GLP-1-mediated anti-inflammatory effects, amelioration of oxidative stress and vascular endothelium protection in the kidney.27–30 In addition, GLP-1 is also involved in sodium and water homeostasis via stimulation of natriuresis and diuresis,31–35 attributed to inhibition of sodium-hydrogen exchange in the proximal tubule.36,37 Recent cardiovascular outcomes studies showed a lower risk of new-onset persistent macroalbuminuria with GLP-1 RAs liraglutide and semaglutide.38,39 To determine the clinical significance of this albuminuria-lowering signal, the effects of dulaglutide should be further evaluated in patients with elevated UACR at baseline.

Limitations of the present study include the inclusion of a small number of participants with low eGFR or high levels of albuminuria. In addition, the studies included in the present analyses were not prospectively designed to evaluate the effects of dulaglutide on kidney function. The study’s strengths include the availability of individual-level data at common timepoints from a large number of participants with T2D, relatively long treatment periods, and the availability of both placebo and active comparator data.

In conclusion, dulaglutide treatment of clinical trial participants with T2D did not affect eGFR and slightly decreased albuminuria; however, because of the limited clinical experience in patients with severely reduced kidney function or end-stage renal disease, the US label indicates that kidney function should be monitored in dulaglutide-treated patients with renal impairment who experience severe gastrointestinal side effects,40 and the European Union label indicates that dulaglutide is not recommended in patients with severely reduced kidney function.41 Effects of dulaglutide treatment in patients with T2D and moderate or severe CKD are being prospectively evaluated in the currently ongoing phase III AWARD-7 study (clinicaltrials.gov NCT01621178).

ACKNOWLEDGMENTS

The authors wish to thank Marie Geissler from INC Research for editorial assistance.

Prior Presentation: portions of these data were presented at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, June 5-9, 2015 and at the 51st Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, September 14-18, 2015.

Conflict of interest

K. D. H., G. A. and F. T. B. are employees of Eli Lilly and Company. J. A. D. is a consultant for Amgen, Aspire Bariatrics, Astra Zeneca, Eli Lilly, Glaxo Smith Kline, Janssen, Merck Sharp and Dohme, Novo Nordisk, REMD Biotherapeutics and Sanofi and is a participant on a Speaker’s Bureau for Astra Zeneca, Janssen, Novo Nordisk and Takeda. K. R. T. is a consultant for Eli Lilly, Amgen, Noxxon. T. D. M. is a retired distinguished medical fellow from Eli Lilly and Company. No other potential conflicts of interest relevant to this article are reported.

Author contributions

K. R. T, T. D. M. and J. A. D. were involved in the interpretation of the data and critically revised the manuscript for important intellectual content and scientific significance. K. R. T also led the development of the revised and final versions of the manuscript. G. A. was involved in the statistical analysis and interpretation of the data and critically revised the manuscript for important intellectual content. K. D. H. was involved in the interpretation of the data and critically revised the manuscript for important intellectual content. F. T. B. was involved in the analysis and interpretation of the data, critically revised the manuscript for important intellectual content and scientific significance, and assisted with drafting and supervising the development of the manuscript. F. T. B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD. Am J Kidney Dis. 2007;49(2):suppl 2:S12-S154.
2. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60(5):850-886.
3. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis. 2014;64(4):510-533.
4. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1121-1127.
5. Jendle J, Grunberger G, Blevins T, Giorgino F, Hietpas RT, Botros FT. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. Diabetes Metab Res Rev. 2016 Apr 21;32(8):776-790. doi: 10.1002/dmrr.2810. Review. PMID: 27102969 [Epub ahead of print].
6. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
7. Davidson JA, Brett J, Falahati A, Scott D. Mild renal impairment and the efficacy and safety of liraglutide. Endocr Pract. 2011;17(3):345-355.
8. Tuttle KR, Heilmann C, Hoogwerf BJ, Brown C, Anderson PW. Effects of exenatide on kidney function, adverse events, and clinical end points of kidney disease in type 2 diabetes. Am J Kidney Dis. 2013;62(2):396-398.
9. Pawaskar M, Tuttle KR, Li Q, Best JH, Anderson PW. Observational study of kidney function and albuminuria in patients with type 2 diabetes treated with exenatide BID versus insulin glargine. Ann Pharmacother. 2014;48(5):571-576.
10. López-Ruiz A, del Peso-Gilsanz C, Meoro-Avilés A, et al. Acute renal failure when exenatide is co-administered with diuretics and angiotensin II blockers. Pharm World Sci. 2010;32(5):539-561.
11. Weise WJ, Sivanandy MS, Block CA, Comi RJ. Exenatide-associated ischemic renal failure. Diabetes Care. 2009;32(2):e22-e23.
12. Kaakeh Y, Kanjee S, Boone K, Sutton J. Liraglutide-induced acute kidney injury. Pharmacotherapy. 2012;32(1):e7-e11.
13. Linnebjerg H, Kothere PA, Park S, et al. Effect of renal impairment on the pharmacokinetics of exendite. Br J Clin Pharmacol. 2007;64(3):317-327.
14. Byetta [prescribing information]. Wilmington, DE: AstraZeneca; 2015.
15. Bydureon [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
16. Lyxumia [summary of product characteristics]. Paris, France: Sanofi-Aventis Group; 2013.
17. Tanzeum [prescribing information]. Wilmington, DE: GlaxoSmithKline LLC; 2014.
18. Victoza [prescribing information]. Princeton, NJ: Novo Nordisk Inc.; 2016.
19. Von Scholten BJ, Hansen TW, Goetze JP, Persson F, Rossing P. Glucagon-like peptide 1 receptor agonist (GLP-1 RA): long-term effect on kidney function in patients with type 2 diabetes. J Diabetes Complications. 2015;29(5):670-674.
20. Muskiet MH, Tonneijck L, Smits MM, et al. Acute renal haemodynamic effects of glucagon-like peptide-1 receptor agonist exenatide in healthy overweight men. Diabetes Obes Metab. 2016;18(2):178-185.
21. Tonneijck L, Smits MM, Muskiet MH, et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. Diabetes. 2016;65(7):1412-1421.
22. Hovind P, Rossing P, Tarnow L, Smidt UM, Parving HH. Progression of diabetic nephropathy. Kidney Int. 2001;59(2):702-709.
23. Hoefield RA, Kalra PA, Baker PG, et al. The use of eGFR and ACR to predict decline in renal function in people with diabetes. Nephrol Dial Transplant. 2011;26(3):887-892.
24. Altempam N, Russell J, El Nahas M. A study of the natural history of diabetic kidney disease (DKD). Nephrol Dial Transplant. 2012;27(5):1847-1854.
25. Hirai A, Imamura S, Hirai K. A novel therapeutic use of glucagon-like peptide1 receptor agonist for the treatment of overt diabetic nephropathy in patients with type 2 diabetes. [Abstract]. Diabetes. 2012;61(suppl 1):A240, A 943-P.
26. Mohan V, Kannan A, Jебarani S. A retrospective analysis of the effect of liraglutide in Asian Indian patients with type 2 diabetes with proteinuria. [Abstract]. Diabetes. 2012;61(suppl 1):A569, A-2249-PO.
27. Fujita H, Morii T, Fujishima H, et al. The protective roles of GLP-1R signaling in diabetic nephropathy: possible mechanism and therapeutic potential. Kidney Int. 2014;85(3):579-589.
28. Imamura S, Hirai K, Hirai A. The glucagon-like peptide-1 receptor agonist, liraglutide, attenuates the progression of overt diabetic nephropathy in type 2 diabetic patients. Tohoku J Exp Med. 2013;231(1):57-61.
29. Park CW, Kim HW, Ko SH, et al. Long-term treatment of glucagon-like peptide-1 analog exendin-4 ameliorates diabetic nephropathy through improving metabolic anomalies in db/db mice. J Am Soc Nephrol. 2007;18(4):1227-1238.
30. Tanaka T, Higashijima Y, Wada T, Nangaku M. The potential for renal protection with incretin-based drugs. Kidney Int. 2014;86(4):701-711.
31. Moreno C, Mistry M, Roman RJ. Renal effects of glucagon-like peptide in rats. Eur J Pharmacol. 2002;434(3):163-167.
32. Gutzwiller JP, Hru P, Huber AR, et al. Glucagon-like peptide-1 is involved in sodium and water homeostasis in humans. Digestion. 2006;73:142-150.
33. Gutzwiller JP, Tschopp S, Bock A, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. J Clin Endocrinol Metab. 2004;89(6):3055-3061.
34. Skov J, Dejgaard A, Frøkjaer J, et al. Glucagon-like peptide-1 (GLP-1): effect on kidney hemodynamics and renin-angiotensin-aldosterone system in healthy men. J Clin Endocrinol Metab. 2013;98(4):E664-E671.
35. Lovshin JA, Barnie A, DeAlmeida A, Logan A, Zinman B, Drucker DJ. Liraglutide promotes natriuresis but does not increase circulating levels of atrial natriuretic peptide in hypertensive subjects with type 2 diabetes. Diabetes Care. 2015;38(1):132-139.
36. Schlatter P, Beglinger C, Drew J, Gutmann H. Glucagon-like peptide 1 receptor expression in primary porcine proximal tubular cells. Regul Pept. 2007;141(1-3):120-128.
37. Carraro-Lacroix LR, Mainic G, Girardi AC. Regulation of Na+/H+ exchanger NHE3 by glucagon-like peptide 1 receptor agonist exendin-4 in renal proximal tubule cells. Am J Physiol Renal Physiol. 2009;297(6):F1647-F1655.
38. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-322.
39. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016 Sep 15. PMID: 27633186 [Epub ahead of print].
40. Trulicity [prescribing information]. Indianapolis, IN: Lilly USA, LLC; 2015.
41. Trulicity [summary of product characteristics]. Houten, The Netherlands: Eli Lilly and Company; 2014.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Tuttle KR, McKinney TD, Davidson JA, Anglin G, Harper KD and Botros FT. Effects of once-weekly dulaglutide on kidney function in patients with type 2 diabetes in phase II and III clinical trials. Diabetes Obes Metab, 2017;19(3):436–441.