Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly alone, or dapagliflozin alone added to metformin monotherapy in subgroups of patients with type 2 diabetes in the DURATION-8 randomized controlled trial

Juan P. Frías MD1 | Elise Hardy MD2 | Azazuddin Ahmed MD3 | Peter Öhman MD2 | Serge Jabbour MD4 | Hui Wang PhD2 | Cristian Guja MD5

1National Research Institute, Los Angeles, California
2AstraZeneca, Gaithersburg, Maryland
3Division of Endocrinology, Diabetes and Metabolic Diseases, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania
4Department of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

This analysis assessed whether responses with exenatide once weekly plus dapagliflozin (n = 231), exenatide once weekly alone (n = 230), or dapagliflozin alone (n = 233) differed in key patient subpopulations of the DURATION-8 trial. Potential treatment-by-subgroup interactions for changes in glycated haemoglobin (HbA1c) and body weight after 28 weeks were evaluated among subgroups determined by baseline HbA1c, age, sex, body mass index, type 2 diabetes duration, race, ethnicity and estimated glomerular filtration rate (eGFR). Exenatide once weekly plus dapagliflozin reduced HbA1c and body weight across all subgroups: least-squares mean reductions ranged from −8.4 to −26.1 mmol/mol (−0.77% to −2.39%) for HbA1c and from −2.07 to −4.55 kg for body weight. Potential treatment-by-subgroup interactions (P < .10) were found for HbA1c change by age (P = .016) and eGFR (P = .097). Age subgroup analysis findings were not consistent with expected mechanistic effects, with the small number of patients aged ≥65 years (n = 74 vs n = 499 for patients aged <65 years) limiting the interpretability of the interaction term. In the exenatide once weekly plus dapagliflozin and dapagliflozin groups, but not the exenatide once weekly group, HbA1c reductions were greater among patients with eGFR ≥90 vs ≥60 to <90 mL/min/1.73 m² (least-squares mean reductions of −23.6 vs −19.0 mmol/mol [−2.16% vs −1.74%], −17.3 vs −12.0 mmol/mol [−1.58% vs −1.10%], and −17.7 vs −16.9 mmol/mol [−1.62% vs −1.55%] for the respective treatments); this was consistent with the mechanism of action of dapagliflozin. A potential treatment-by-subgroup interaction was observed for change in body weight by sex (P = .099), with greater weight loss for women vs men across all treatments (range −2.56 to −3.98 kg vs −0.56 to −2.99 kg). In conclusion, treatment with exenatide once weekly plus dapagliflozin reduced HbA1c and body weight across all patient subgroups and was more effective than exenatide once weekly or dapagliflozin alone in all adequately sized subgroups.

KEYWORDS
dapagliflozin, exenatide, GLP-1 analogue, SGLT2 inhibitor, type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive illness with a strong genetic component that is caused by defects in multiple organ systems.1 Comorbidities and chronic complications are highly prevalent among people with T2DM,2 necessitating a multifactorial approach to management. In addition, other characteristics (such as age, sex, duration of disease, race and ethnicity) require individualization of patient care.1–5

Because of the progressive nature of T2DM, most patients will eventually require multiple therapies to achieve and maintain their individualized therapeutic targets.4 Several glucose-lowering drug
classes with complementary mechanisms of action are available. Two of the most recent classes are the glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the sodium-glucose co-transporter-2 (SGLT2) inhibitors. The DURATION-8 (Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once Weekly) trial showed that simultaneous initiation of the GLP-1RA exenatide once weekly and the SGLT2 inhibitor dapagliflozin improved glycaemic control, systolic blood pressure and body weight over 28 weeks compared with exenatide once weekly or dapagliflozin alone in patients with T2DM inadequately controlled by metformin.6 The aim of the present analysis was to determine whether the differences in glycated haemoglobin (HbA1c) and body weight responses seen in the overall population of DURATION-8 differed among key patient subpopulations.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an analysis of data from the DURATION-8 study (ClinicalTrials.gov identifier: NCT02229396), the methods of which have previously been reported.6 DURATION-8 enrolled adults (aged ≥18 years) with T2DM and inadequate glycaemic control (HbA1c 6.5-10.8 mmol/mol [8.0%-12.0%]) despite receiving metformin monotherapy at a stable dose (≥1500 mg/d) for at least 2 months before screening. Patients were randomized to receive subcutaneous exenatide 2 mg once weekly in combination with oral dapagliflozin 10 mg once daily, exenatide once weekly plus oral placebo once daily, or dapagliflozin once daily plus subcutaneous placebo once weekly, all administered with background metformin, for 28 weeks.

The original study protocol was developed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the ethics and regulatory committees and institutional review boards of the participating institutions.6 All patients provided written informed consent.

2.2 | Study outcomes and patient subgroups

The primary endpoint of DURATION-8 was change in HbA1c from baseline to week 28, while change in body weight from baseline to week 28 was a secondary endpoint. In this analysis, changes from baseline to week 28 in HbA1c and body weight were assessed in various patient subgroups. Subgroups were defined by baseline HbA1c (<8.0%, ≥8.0% to <9.0%, or ≥9.0% [<64, ≥64 to <75, or ≥75 mmol/mol]), age (<65 or ≥65 years), sex, body mass index (BMI; <25, ≥25 to <30, or ≥30 kg/m²), T2DM duration (<3, ≥3 to ≤10, or >10 years), race (white, black/African American, Asian, American Indian/Alaskan native, or all other races), ethnicity (Hispanic/Latino or not Hispanic/Latino), and estimated glomerular filtration rate (eGFR; <60, ≥60 to <90, or ≥90 mL/min/1.73 m²).

2.3 | Statistical analysis

Least-squares mean changes in HbA1c and body weight for treatment groups were calculated using a mixed-effects model for repeated measures analysis, with treatment, country, baseline HbA1c stratum, baseline HbA1c and body weight, week, subgroup, treatment-by-week, subgroup-by-week, subgroup-by-treatment, and subgroup-by-week-by-treatment interactions as fixed factors. Nominal P values for treatment-by-subgroup interactions were reported, with P < .10 considered indicative of a potential treatment-by-subgroup interaction; this conservative threshold is commonly employed to ensure adequate sensitivity to detect interactions because of the reduced power within subgroups. There was no correction for multiplicity.

3 | RESULTS

Of 695 randomized patients, one did not receive study medication, leaving 231, 230 and 233 patients in the exenatide once weekly plus dapagliflozin, exenatide once weekly and dapagliflozin groups, respectively. Baseline characteristics were similar among treatment groups, with the exception of fewer women in the exenatide once weekly group and fewer Hispanic/Latino patients in the dapagliflozin group.6

3.1 | Change in HbA1c

Clinically relevant HbA1c reductions were observed with all treatments across all subgroups. HbA1c reductions were greater with exenatide once weekly plus dapagliflozin than with either exenatide once weekly or dapagliflozin alone in all adequately sized subgroups. After 28 weeks, HbA1c was reduced with all treatments across all baseline HbA1c subgroups, with no evidence of a treatment-by-subgroup interaction (P = .978; Table 1). HbA1c reductions were greater with increasing baseline HbA1c. Small numbers of patients in the HbA1c <8.0% (<64 mmol/mol) subgroup limited the interpretability of the interaction P value.

A potential treatment-by-subgroup interaction was observed for HbA1c change by baseline age subgroup (P = .016; Figure 1A), although there were too few patients aged ≥65 years in each treatment group for this to be conclusive. HbA1c reductions were greater for patients aged ≥65 years vs <65 years with exenatide once weekly plus dapagliflozin, while this relationship was reversed for exenatide once weekly alone and dapagliflozin alone (Figure 1A).

Reductions in HbA1c were observed in all treatment groups across all baseline BMI and T2DM duration subgroups (Table 1), with no evidence of treatment-by-subgroup interactions. By contrast, a potential treatment-by-subgroup interaction was observed for HbA1c change by baseline eGFR (P = .097; Figure 1B). HbA1c reductions were greater for patients with eGFR ≥90 mL/min/1.73 m² vs ≥60 to <90 mL/min/1.73 m² in the exenatide once weekly plus dapagliflozin and dapagliflozin alone groups, whereas this pattern was not observed with exenatide once weekly alone. In addition, sex, race or ethnicity did not differentially affect the improvements in HbA1c observed with the three treatments (Table 1); however, the interpretability of the interaction term for the race subgroup was limited by the small numbers in some of the race subgroups.
TABLE 1  Change in HbA1c (mmol/mol) from baseline to week 28 by subgroup

| Baseline subgroup | Exenatide once weekly + dapagliflozin | Exenatide once weekly + placebo | Dapagliflozin + placebo | Interaction value |
|-------------------|---------------------------------------|---------------------------------|-------------------------|------------------|
| HbA1c (<8.0% (<64 mmol/mol) | (11/74/108) | (13/71/100) | (14/76/106) | .978 |
| ≥8.0 to <9.0% (<64 to <75 mmol/mol) | -16.7 ± 4.2 | -7.5 ± 3.9 | -10.8 ± 3.8 | |
| ≥9.0% (≥75 mmol/mol) | -18.0 ± 1.6 | -13.7 ± 1.6 | 10.7 ± 1.6 | |
| BMI (n for subgroups) (13/63/117) | (12/65/107) | (12/49/135) | .906 |
| <25 kg/m² | -23.1 ± 3.7 | -20.4 ± 3.8 | -20.1 ± 3.9 | |
| ≥25 to <30 kg/m² | -20.6 ± 1.7 | -16.5 ± 1.7 | -14.1 ± 2.0 | |
| ≥30 kg/m² | -22.1 ± 1.3 | -17.8 ± 1.3 | -15.1 ± 1.2 | |
| Sex (n for subgroups) (84/109) | (96/88) | (93/103) | .550 |
| Men | -21.0 ± 1.5 | -17.7 ± 1.4 | -15.8 ± 1.4 | |
| Women | -22.2 ± 1.3 | -17.4 ± 1.4 | -14.6 ± 1.4 | |
| Race (n for subgroups) (161/28/3/0/1) | (161/20/1/2/0) | (165/24/1/0/6) | .918 |
| White | -21.3 ± 1.2 | -17.3 ± 1.2 | -15.0 ± 1.2 | |
| Black/African American | -23.6 ± 2.6 | -18.8 ± 3.0 | -13.3 ± 2.6 | |
| Asian | -8.4 ± 8.3 | -17.7 ± 14.4 | -15.3 ± 14.4 | |
| American Indian/Alaskan Native | -9.1 ± 10.2 | - | - |
| Other | -19.1 ± 14.4 | -24.8 ± 5.9 | |
| Ethnicity (n for subgroups) (76/117) | (68/116) | (72/124) | .396 |
| Hispanic/Latino | -17.9 ± 1.6 | -14.8 ± 1.7 | -14.6 ± 1.7 | |
| Non-Hispanic/Latino | -23.5 ± 1.3 | -18.7 ± 1.3 | -15.0 ± 1.2 | |
| T2DM duration (n for subgroups) (42/100/51) | (42/101/41) | (40/110/46) | .633 |
| <3 years | -24.4 ± 2.2 | -20.6 ± 2.2 | -19.5 ± 2.1 | |
| ≥3 to ≤10 years | -20.3 ± 1.4 | -16.9 ± 1.4 | -14.4 ± 1.3 | |
| >10 years | -21.5 ± 2.0 | -16.0 ± 2.1 | -12.4 ± 2.1 | |

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; T2DM, type 2 diabetes mellitus. Data are least-squares mean ± standard error, unless otherwise specified. Conversion calculator for HbA1c (mmol/mol to %): http://www.ngsp.org/convert2.asp

a Study inclusion criteria required patients to have an HbA1c of 64 to 108 mmol/mol (8.0%-12.0%) at screening, but HbA1c decreased to <64 mmol/mol (<8.0%) between screening and baseline measurements in some patients.

3.2 | Change in body weight

Body weight decreased from baseline with all three treatments in all subgroups (Table S1); greater reductions were seen with exenatide once weekly plus dapagliflozin than with exenatide once weekly or dapagliflozin alone across all adequately sized subgroups. A potential treatment-by-subgroup interaction was found for sex (P = .099; Table S1), related to the smaller reduction in body weight observed among men in the group receiving exenatide once weekly alone. In all treatment groups, body weight reductions were greater for women than men. Reductions in body weight were numerically greater for patients with baseline HbA1c ≥8.0% to <9.0% (≥64 to <75 mmol/mol) compared with ≥9.0% (≥75 mmol/mol) in the groups receiving exenatide once weekly plus dapagliflozin or exenatide once weekly alone, although evidence of a treatment-by-subgroup interaction (P = .918) was not observed. As with the analysis of HbA1c change, small patient numbers in the HbA1c <8.0% (<64 mmol/mol) subgroup limited the interpretability of the interaction P value in this subgroup.

4 | DISCUSSION

The results of the present analysis show that the combination of exenatide once weekly plus dapagliflozin was effective in reducing HbA1c and body weight irrespective of sex, age, body weight, race, ethnicity or disease characteristics. While a potential treatment-by-subgroup interaction was observed between age and the HbA1c change, the subgroup of patients aged ≥65 years was small, which limited the interpretability of the interaction term. Moreover, the results did not suggest a mechanistic explanation for differences according to age and, therefore, should be interpreted with caution. As expected, a potential treatment-by-subgroup interaction was observed for change in HbA1c by eGFR in the dapagliflozin-containing treatment groups; HbA1c reductions were greater for patients with eGFR ≥90 mL/min/1.73 m² vs eGFR >90 mL/min/1.73 m², consistent with the mechanism of action of dapagliflozin, which blocks the reabsorption of glucose in the kidney and is dependent on plasma glucose and glomerular filtration rate. The small number of patients with eGFR <60 mL/min/1.73 m² limited the interpretability of these findings. Weight loss appeared greater for patients with baseline HbA1c ≥8.0% to <9.0% (≥64 to <75 mmol/mol) vs ≥9.0% (≥75 mmol/mol), potentially because higher baseline HbA1c was associated with a catabolic state and weight loss was attenuated by improved glycemic control, with improvement in catabolic state; there were few patients with baseline HbA1c <8.0% (<64 mmol/mol), which limits the interpretability of the interaction P value. Finally, there was evidence of a potential interaction between sex and body weight change.
Weight loss was greater among women than men; however, this potential interaction may be related to the smaller-than-expected weight loss in men receiving exenatide once weekly.

As expected, the combination of exenatide once weekly plus dapagliflozin reduced HbA1c and body weight more than either drug alone across all adequately sized subgroups. This was consistent with the results for the overall study population, in which exenatide once weekly plus dapagliflozin produced significantly greater reductions in HbA1c and body weight than exenatide once weekly or dapagliflozin alone (−21.9 vs −17.5 and −15.3 mmol/mol [−2.0%, −1.6% and −1.4%] and −3.55 vs −1.56 and −2.22 kg, respectively). To date, the DURATION-8 study is the only randomized controlled trial of an SGLT2 inhibitor and GLP-1RA combination in patients with T2DM for which results have been published. However, another study examined the effects of this combination in individuals with obesity without T2DM and found that those treated with exenatide once weekly plus dapagliflozin had a significantly greater reduction in body weight after 24 weeks than the placebo group (−4.48 vs −0.35 kg, respectively). Results from the AWARD-10 study (NCT02597049), when available, will provide further information on the effects of combination therapy with these two glucose-lowering therapy classes.

This analysis was not designed to make statistical comparisons between treatments within each subgroup or to identify subgroups in

![FIGURE 1 Glycated haemoglobin (HbA1c) decrease from baseline to week 28 according to A, baseline age subgroups (<65 or ≥65 years) and B, baseline estimated glomerular filtration rate (eGFR) subgroups (<60, ≥60 to <90, or ≥90 mL/min/1.73 m²). LSM, least-squares mean; SE, standard error. Conversion calculator for HbA1c (mmol/mol to %): http://www.ngsp.org/convert2.asp]
which a treatment was more or less effective than in the overall intention-to-treat population; however, to the best of our knowledge, this is the first analysis evaluating potential treatment-by-subgroup interactions for concomitant administration of a GLP-1RA/SGLT2 inhibitor combination in patients with T2DM. Furthermore, there are several published reports investigating the effects of a GLP-1RA or SGLT2 inhibitor individually according to various baseline characteristics.

Analyses of exenatide twice daily treatment have shown that reductions in HbA1c and body weight are generally unaffected by baseline HbA1c or baseline BMI,18-10, however, one study found that patients with a T2DM duration of >15 years lost more weight with exenatide twice daily vs placebo than patients with a shorter disease duration.8 In a study investigating exenatide twice daily and once weekly, HbA1c reductions with exenatide twice daily were greater among Asian patients vs white patients (P < .0001), but weight loss was greater among white patients.11 There was no effect of race on HbA1c reduction with exenatide once weekly in this study, although white patients lost more weight than Asian patients with exenatide once weekly.13 A pooled analysis of the effect of exenatide once weekly according to age, sex, race, T2DM duration, and BMI showed no differences in HbA1c and body weight reductions in any of the subpopulations investigated.12 Although some studies investigating treatment with exenatide twice daily10 or dulaglutide13 showed no impact of sex on the change in body weight in people with T2DM, recent analyses of dulaglutide data found weight loss was greater for women than men.14,15

There are also studies evaluating the effect of baseline characteristics on SGLT2 inhibitor efficacy. Analyses of canagliflozin data suggest that reductions in HbA1c and body weight with canagliflozin are not affected by race;16,17 however, HbA1c reductions were greater in patients with a higher baseline HbA1c than those with a lower baseline HbA1c.18 A pooled analysis of the effect of dapagliflozin on cardiovascular risk factors according to eGFR confirmed the decreased efficacy in reducing HbA1c among patients with eGFR ≥45 to <60 mL/min/1.73 m² compared with those with eGFR ≥60 to <90 or ≥ 90 mL/min/1.73 m² (interaction P < .001), with no influence on the effect of treatment on body weight.19 Finally, an interim analysis of the ASSIGN-K study showed no relationship between sex and weight loss in Japanese patients with T2DM.20

The present analysis has some limitations. Primarily, the small size of some subpopulations limited the interpretability of the results. Some weight analyses were performed post hoc, with the inherent limitations of such analyses. Furthermore, there was no adjustment for multiplicity.

In conclusion, treatment with exenatide once weekly plus dapagliflozin reduced HbA1c and body weight across all patient subgroups and was more effective than exenatide once weekly or dapagliflozin alone in all adequately sized subgroups. This was consistent with the results for the overall study population. Potential treatment-by-subgroup interactions were observed for age and eGFR when evaluating changes in HbA1c, and for sex when evaluating changes in body weight. No other treatment-by-subgroup interactions were observed.

ACKNOWLEDGMENTS
Sheridan Henness, PhD, and Simone Boniface of inScience Communications, Springer Healthcare (Auckland, New Zealand) provided medical writing support in accordance with Good Publication Practice, funded by AstraZeneca.

Conflict of interest
J. P. F. has received research support from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, IONIS, Janssen, Johnson & Johnson, Ligand, Merck, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi, Theracos and vTv Therapeutics, and has participated in the scientific advisory boards for and received consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk, Sanofi and Theracos. E. H. and P. Ö. are employees of AstraZeneca. A. A. has received research grants to conduct clinical trials from AbbVie, AstraZeneca, Kowa Pharmaceuticals, Novo Nordisk and Sanofi Aventis. S. J. has acted as a consultant for AstraZeneca, Eli Lilly and Janssen. H. W. is a consultant for AstraZeneca. C. G. has participated in scientific advisory boards for and received consulting fees from Alfa Wasserman, AstraZeneca, Bayer AG, Berlin-Chemie Menwarin, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi.

Author contributions
J. P. F., E. H., A. A., P. Ö., S. J. and C. G. contributed to the acquisition of study data and the analysis and interpretation of the data. J. P. F., A. A., S. J. and C. G. were study investigators. H. W. contributed to the analysis and interpretation of the data. All authors provided critical review of the manuscript and read and approved the final version.

ORCID
Juan P. Frías http://orcid.org/0000-0001-9486-1255
Serge Jabbour http://orcid.org/0000-0002-4080-0470
Cristian Guja http://orcid.org/0000-0002-8703-0522

REFERENCES
1. American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care. 2017;40:S1-S135.
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35: 1364-1379.
3. Bailey CJ, Day C. Diabetes therapies in renal impairment. Br J Diabetes Vasc Dis. 2012:12:167-171.
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38:140-149.
5. Clemens KK, Liu K, Shariff S, Schernthaner G, Tangri N, Garg AX. Secular trends in antihyperglycaemic medication prescriptions in older adults with diabetes and chronic kidney disease: 2004-2013. Diabetes Obes Metab. 2016;18:607-614.
6. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy
7. Lundkvist P, Sjöström CD, Amini S, Pereira MJ, Johnsson E, Eriksson JW. Dapagliflozin once-daily and exenatide once-weekly dual therapy: a 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. *Diabetes Obes Metab.* 2017;19:49-60.

8. Rosenstock J, Shenunda SK, Bergenstal RM, et al. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes. *Diabetes Care.* 2012;35:955-958.

9. Wolffenbuttel BH, Van Gaal L, Duran-Garcia S, Han J. Relationship of body mass index with efficacy of exenatide twice daily added to insulin glargine in patients with type 2 diabetes. *Diabetes Care.* 2012;35:955-958.

10. Pencek R, Blickensderfer A, Li Y, Brunell SC, Anderson PW. Exenatide twice daily: analysis of effectiveness and safety data stratified by age, sex, race, duration of diabetes, and body mass index. *Postgrad Med.* 2012;124:21-32.

11. Sheu WH, Brunell SC, Blase E. Efficacy and tolerability of exenatide twice daily and exenatide once weekly in Asian versus white patients with type 2 diabetes mellitus: a pooled analysis. *Diabetes Res Clin Pract.* 2016;114:160-172.

12. Pencek R, Blickensderfer A, Li Y, Brunell SC, Chen S. Exenatide once weekly for the treatment of type 2 diabetes: effectiveness and tolerability in patient subpopulations. *Int J Clin Pract.* 2012;66:1021-1032.

13. Umpierrez GE, Pantalone KM, Kwan AY, Zimmermann AG, Zhang N, Fernandez Lando L. Relationship between weight change and glycaemic control in patients with type 2 diabetes receiving once-weekly dulaglutide treatment. *Diabetes Obes Metab.* 2016;18:615-622.

14. Gallwitz B, Dagogo-Jack S, Thieu V, et al. Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c. *Diabetes Obes Metab.* 2018;20:409-418.

15. Onishi Y, Oura T, Nishiyma H, Ohyama S, Takeuchi M, Iwamoto N. Subgroup analysis of phase 3 studies of dulaglutide in Japanese patients with type 2 diabetes. *Endocr J.* 2016;63:263-273.

16. Davidson JA, Aguilar R, Lavalle Gonzalez FJ, et al. Efficacy and safety of canagliflozin in type 2 diabetes patients of different ethnicity. *Ethn Dis.* 2016;26:221-228.

17. Gavin JR III, Davies MJ, Davies M, Vijapurkar U, Alba M, Meininger G. The efficacy and safety of canagliflozin across racial groups in patients with type 2 diabetes mellitus. *Curr Med Res Opin.* 2015;31:1693-1702.

18. Wilding JP, Blonde L, Leiter LA, et al. Efficacy and safety of canagliflozin by baseline HbA1c and known duration of type 2 diabetes mellitus. *J Diabetes Complications.* 2015;29:438-444.

19. Petrykiv S, Sjöström CD, Greasley PJ, Xu J, Persson F, Heerspink HJL. Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. *Clin J Am Soc Nephrol.* 2017;12:751-759.

20. Iemitsu K, Izuka T, Takihata M, et al. Factors influencing changes in hemoglobin A1c and body weight during treatment of type 2 diabetes with ipragliflozin: interim analysis of the ASSIGN-K study. *J Clin Med Res.* 2016;8:373-378.

**SUPPORTING INFORMATION**

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