Improved Glucose Control With Weight Loss, Lower Insulin Doses, and No Increased Hypoglycemia With Empagliflozin Added to Titrated Multiple Daily Injections of Insulin in Obese Inadequately Controlled Type 2 Diabetes

Julio Rosenstock,[1] Ante Jelaska,[2] Guillaume Frappin,[3] Afshin Salsali,[2] Gabriel Kim,[4] Hans J. Woerle,[4] and Uli C. Broedl,[4] on behalf of the EMPA-REG MDI Trial Investigators

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OBJECTIVE

We investigated the efficacy and safety of the sodium glucose cotransporter 2 inhibitor, empagliflozin, added to multiple daily injections of insulin (MDI insulin) in obese patients with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

Patients inadequately controlled on MDI insulin ± metformin (mean HbA_{1c} 8.3% [67 mmol/mol]; BMI 34.8 kg/m^2; insulin dose 92 international units/day) were randomized and treated with once-daily empagliflozin 10 mg (n = 186), empagliflozin 25 mg (n = 189), or placebo (n = 188) for 52 weeks. Insulin dose was to remain stable in weeks 1–18, adjusted to meet glucose targets in weeks 19–40, then stable in weeks 41–52. The primary end point was change from baseline in HbA_{1c} at week 18. Secondary end points were changes from baseline in insulin dose, weight, and HbA_{1c} at week 52.

RESULTS

Adjusted mean ± SE changes from baseline in HbA_{1c} were −0.50 ± 0.05% (−5.5 ± 0.5 mmol/mol) for placebo versus −0.94 ± 0.05% (−10.3 ± 0.5 mmol/mol) and −1.02 ± 0.05% (−11.1 ± 0.5 mmol/mol) for empagliflozin 10 mg and empagliflozin 25 mg, respectively, at week 18 (both $P < 0.001$). At week 52, further reductions with insulin titration resulted in changes from baseline in HbA_{1c} of −0.81 ± 0.08% (−8.9 ± 0.9 mmol/mol), −1.18 ± 0.08% (−12.9 ± 0.9 mmol/mol), and −1.27 ± 0.08% (−13.9 ± 0.9 mmol/mol) with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively, and final HbA_{1c} of 7.5% (58 mmol/mol), 7.2% (55 mmol/mol), and 7.1% (54 mmol/mol), respectively. More patients attained HbA_{1c} <7% (<53 mmol/mol) with empagliflozin (31–42%) versus placebo (21%; both $P < 0.01$). Empagliflozin 10 mg and empagliflozin 25 mg reduced insulin doses (−9 to −11 international units/day) and weight (−2.4 to −2.5 kg) versus placebo (all $P < 0.01$) at week 52.

CONCLUSIONS

In obese, difficult-to-treat patients with T2DM inadequately controlled on high MDI insulin doses, empagliflozin improved glycemic control and reduced weight without increasing the risk of hypoglycemia and with lower insulin requirements.

[1]*Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX*
[2]*Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT*
[3]*Boehringer Ingelheim France, Reims, France*
[4]*Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany*

Corresponding author: Julio Rosenstock, juliorosenstock@dallasdiabetes.com.

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A slide set summarizing this article is available online.

Guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend the initiation of basal insulin, usually in conjunction with oral antidiabetes agents, in patients with type 2 diabetes mellitus (T2DM) who have marked hyperglycemia when it is unlikely that another drug will be of sufficient additional benefit (1). However, in clinical practice, insulin therapy is often delayed or not optimized. Barriers to the initiation and optimization of insulin therapy include fear of hypoglycemia and weight gain and concerns over the complexity of the treatment regimen (2,3). Approximately 40–50% of patients with T2DM fail to achieve glycemic control with basal insulin plus oral antidiabetes agents after 24 weeks of treatment (4). Further intensification of the insulin regimen to control hyperglycemia is traditionally achieved with progressive additions of prandial insulin up to multiple daily injections of insulin (MDI insulin). However, MDI insulin is overwhelming for most patients, and despite combination with metformin, insulin requirements are often high and patients are still unable to achieve glycemic control. In addition, these patients are typically insulin resistant (5), and comorbidities such as obesity and hypertension are very common. Weight gain associated with the use of high insulin doses may make it even more difficult to achieve glycemic control (5). Accordingly, there is a high unmet need for antidiabetes therapies that can be used in combination with MDI insulin to improve glycemic control in patients with T2DM without exacerbating comorbidities.

Empagliflozin, a potent and selective sodium glucose cotransporter 2 (SGLT2) inhibitor (6), reduces hyperglycemia by reducing renal glucose reabsorption, causing urinary glucose excretion (7). In phase III studies, empagliflozin used as monotherapy or as an add-on to metformin, metformin plus sulfonylurea, pioglitazone (with or without metformin), or basal insulin improved glycemic control and consistently reduced body weight and blood pressure (8–12). Empagliflozin is potentially an attractive option for use in combination with insulin, as its mechanism of action is independent of β-cell function (13), it generates weight loss, and it is associated with a low risk of hypoglycemia (8–12).

The EMPA-REG MDI trial was undertaken to evaluate the efficacy and safety of empagliflozin 10 mg and empagliflozin 25 mg versus placebo as an add-on to MDI insulin with or without metformin for 52 weeks in patients with T2DM and insufficient glycemic control. We hypothesized that empagliflozin would improve glycemic control and body weight in this difficult-to-treat, obese population of patients with T2DM and high insulin requirements.

RESEARCH DESIGN AND METHODS

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted from March 2011 to April 2013 in 104 centers across 14 countries. The clinical trial protocol was approved by the institutional review boards and independent ethics committees and competent authorities of the participating centers, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. The trial was registered with ClinicalTrials.gov (NCT01306214). All patients provided written informed consent.

Inclusion and Exclusion Criteria

This study enrolled obese adults (BMI $\geq$30 and $\leq$45 kg/m^2) with T2DM and insufficient glycemic control (HbA$_{1c}$ $\geq$7.5 to $\leq$10% [$\geq$58 to $\leq$86 mmol/mol] at screening) despite diet and exercise counseling and treatment with MDI insulin (total daily dose $>$60 international units) alone or in combination with metformin (immediate or extended release, $\geq$1,500 mg/day, maximum tolerated dose, or maximum dose according to the local label). For $\geq$12 weeks prior to randomization, insulin dose was not to be changed by $>$10% and metformin dose was to be unchanged. Premixed insulins were not permitted.

Exclusion criteria included uncontrolled hyperglycemia (glucose level $>$13.3 mmol/L after an overnight fast during the placebo run-in, confirmed by a second measurement); acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; indication of liver disease; impaired renal function during screening or run-in (estimated glomerular filtration rate [eGFR] using the modification of diet and renal disease equation $<$60 mL/min/1.73 m^2); gastrointestinal surgeries that induce malabsorption; history of cancer (except for basal cell carcinoma) within 5 years; disorders causing hemolysis or unstable erythrocytes; treatment with systemic steroids at time of consent; change in dosage of thyroid hormones within 6 weeks prior to consent; treatment with antiobesity drugs or alcohol or drug abuse within 3 months of consent; and investigational drug intake within 30 days of intake of study drug.

Treatment and Interventions

Following a 2-week, open-label, placebo run-in period, patients still meeting the inclusion/exclusion criteria were randomized (1:1:1) to receive once-daily empagliflozin 10 mg, empagliflozin 25 mg, or placebo as an add-on to MDI insulin, with or without metformin, for 52 weeks. Randomization was undertaken using a third-party interactive voice- and web-response system and was stratified by HbA$_{1c}$ ($<$8.5, $\geq$8.5% [$<$69, $\geq$69 mmol/mol]), eGFR (chronic kidney disease stage 1, $\geq$90 mL/min/1.73 m^2; chronic kidney disease stage 2, 60–89 mL/min/1.73 m^2), region (Europe, North America, Latin America), and background antidiabetes therapy (insulin alone, insulin plus metformin). Patients received diet and exercise counseling based on local recommendations at the start of the run-in period and were reminded to follow their diet and exercise plan at every study visit. For the first 18 weeks, the total daily dose of insulin was to remain within 10% of the prescribed dose at randomization. During the titrated treat-to-target period (weeks 19–40), insulin dose was to be adjusted to achieve a preprandial glucose target of $<$5.5 mmol/L ($<$100 mg/dL) and a postprandial glucose target of $<$7.8 mmol/L ($<$140 mg/dL). Between weeks 41 and 52, the total daily dose of insulin was to remain within 10% of the insulin dose prescribed at week 40, except for adjustments for safety reasons. Metformin dose was to remain unchanged throughout the study. Study visits were scheduled at screening; the start of the placebo run-in; randomization; after 4, 8, 12, 18, 24, 32, 40, 46, and 52 weeks of treatment; and 4 weeks after the last dose of study drug.

Rescue could be initiated at any time during the treatment period if a patient had hypoglycemia that would put them at risk. During weeks 1–12, rescue medication could be initiated if a patient had a glucose level of >13.3 mmol/L (>240 mg/dL) after an overnight fast. During weeks 13–24, rescue therapy could be initiated if confirmed fasting glucose levels were >11.1 mmol/L (>200 mg/dL). During weeks 24–52, rescue therapy could be initiated if a patient had a confirmed glucose level >10.0 mmol/L (>180 mg/dL) after an overnight fast or HbA_{1c} >8.0% (>64 mmol/mol) after an overnight fast. The initiation, choice (excluding other SGLT2 inhibitors), and dosage of rescue medication were at the discretion of the investigator according to local prescribing information. Changes in dose of metformin for ≥7 days or addition of a new antidiabetes agent for ≥7 days were considered rescue therapy. Before week 18, changes in total insulin daily dose >10% of the baseline dose for ≥7 days were considered rescue therapy; changes in insulin dose were not considered rescue therapy for the efficacy analyses after week 18.

End Points and Assessments

The primary end point was the change from baseline in HbA_{1c} at week 18. Secondary end points were changes from baseline at week 52 in insulin daily dose, body weight, and HbA_{1c}. Exploratory end points included changes from baseline in body weight at week 18; changes from baseline at weeks 18 and 52 in fasting plasma glucose (FPG), systolic blood pressure (SBP), and diastolic blood pressure (DBP); percentage of patients with HbA_{1c} ≥7% (≥53 mmol/mol) at baseline who had HbA_{1c} <7% at weeks 18 and 52; and use of rescue therapy.

Safety end points included vital signs, clinical laboratory parameters, and adverse events (AEs) up to 7 days after the last dose of study drug (preferred terms coded according to the Medical Dictionary for Drug Regulatory Activities version 15.1). AEs of special interest included confirmed hypoglycemic AEs (plasma glucose ≤3.9 mmol/L and/or requiring assistance) and events consistent with urinary tract and genital infections identified using prospectively defined search categories based on 73 and 89 preferred terms, respectively.

Statistical Analysis

Sample size calculations indicated that 555 patients (185 per treatment group) would provide 90% power to detect a difference between empagliflozin and placebo in the primary end point with a two-sided significance level of 0.025, assuming a dropout of 15%.

The primary efficacy analysis was performed on the full analysis set (FAS), which included patients treated with ≥1 dose of study drug who had a baseline HbA_{1c} value. Secondary end points and changes in insulin dose corrected for body weight were analyzed in the "PPS-completers-52" set, defined as patients in the FAS who were on treatment up to day 357 and did not have important protocol violations (such as changes in insulin dose of >10% of prescribed dose at week 40 for ≥7 days during the last 12 weeks). Efficacy analyses of other end points were performed on the FAS at week 18 and in the PPS-completers-52 set at week 52. Safety analyses were performed on the treated set (patients treated with ≥1 dose of study drug).

The primary end point was assessed using an ANCOVA model, with treatment, region, background antidiabetes therapy, and eGFR as fixed effects and baseline HbA_{1c} as a linear covariate. Secondary end points, continuous exploratory end points, and changes in insulin dose corrected for body weight were analyzed using the statistical model described for the primary end point, with the baseline value for the end point in question as an additional linear covariate. Categorical change in HbA_{1c} was analyzed using logistic regression including the same factors as covariates.

Values after rescue therapy were set to missing and imputed using the last observation carried forward (LOCF) approach, except for the analysis of lipid parameters, for which LOCF was used and values after rescue therapy were included (LOCF-IR). Changes over time in HbA_{1c} and insulin daily dose were analyzed using restricted maximum likelihood–based mixed-model repeated measures (MMRM) using observed cases (OCs). Categorical response in HbA_{1c} was analyzed using a noncompleters considered failures imputation, which assumed that patients who prematurely discontinued the trial and/or received rescue therapy did not achieve the HbA_{1c} target.

Treatment differences versus placebo for primary and secondary end points were tested using a hierarchical testing approach for each dose using pairwise comparisons between each dose of empagliflozin and placebo using the adjusted means from the model, at a significance level of 2.5% (two-sided) to maintain the overall type I error at 5% in the following sequence: empagliflozin versus placebo in change from baseline in HbA_{1c} at week 18; empagliflozin versus placebo in change from baseline in insulin dose at week 52; empagliflozin versus placebo in change from baseline in body weight at week 52; empagliflozin versus placebo in change from baseline in HbA_{1c} at week 52 (one-sided noninferiority test at level of 1.25%), empagliflozin versus placebo in change from baseline in HbA_{1c} at week 52 (superiority). Exploratory tests were two-sided at a 5% level (no multiplicity adjustment).

RESULTS

Patients

A total of 563 patients were randomized and treated with placebo (n = 188), empagliflozin 10 mg (n = 186), or empagliflozin 25 mg (n = 189) (Supplementary Fig. 1). Overall, 475 (84%) patients completed the 52-week treatment period. Baseline mean ± SD characteristics shown in Supplementary Table 1 are age 56.7 ± 9.5 years; BMI 34.8 ± 4.1 kg/m^2; FPG 8.52 ± 2.64 mmol/L; HbA_{1c} 8.3 ± 0.7% [67 ± 7.7 mmol/mol], with 33% of patients with HbA_{1c} <8% (<64 mmol/mol) and 23% with HbA_{1c} ≥9% (≥75 mmol/mol); SBP 133.3 ± 15.5 mmHg; DBP 78.8 ± 8.6 mmHg; and baseline insulin dose 92 ± 44 international units. Baseline basal insulin doses were 53 ± 32, 49 ± 23, and 51 ± 25 international units/day with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Baseline prandial insulin doses were 40 ± 29, 40 ± 29, and 41 ± 35 international units/day with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Efficacy: Week 18

During the first 18 weeks of treatment, the total insulin daily dose was to remain within 10% of the prescribed dose at randomization. At week 18, adjusted mean ± SE changes from baseline in HbA_{1c} were

−0.50 ± 0.05% (−5.5 ± 0.5 mmol/mol) with placebo compared with −0.94 ± 0.05% (−10.3 ± 0.5 mmol/mol) with empagliflozin 10 mg and −1.02 ± 0.05% (−11.1 ± 0.5 mmol/mol) with empagliflozin 25 mg ($P < 0.001$ for both) (Table 1, Fig. 1*A*).

Adjusted mean ± SE changes from baseline in FPG were 0.19 ± 0.16 mmol/L with placebo compared with −0.98 ± 0.16 mmol/L with empagliflozin 10 mg and −1.36 ± 0.16 mmol/L with empagliflozin 25 mg at week 18 ($P < 0.001$ vs. placebo for both) (Table 1, Supplementary Fig. 2*A*).

Body weight increased from baseline with placebo (adjusted mean ± SE 0.34 ± 0.18 kg) compared with a decrease with empagliflozin 10 mg (−0.97 ± 0.18 kg) and empagliflozin 25 mg (−1.54 ± 0.18 kg) at week 18 ($P < 0.001$ vs. placebo for both) (Table 1, Fig. 1*B*).

Adjusted mean ± SE changes from baseline in SBP were −1.2 ± 0.8 mmHg with placebo compared with −3.6 ± 0.8 mmHg with empagliflozin 10 mg (P = 0.037). The change from baseline in SBP with empagliflozin 25 mg did not reach significance versus placebo (Supplementary Table 2, Supplementary Fig. 3*A*). Adjusted mean ± SE changes from baseline in DBP did not reach significance for either empagliflozin dose (Supplementary Table 2, Supplementary Fig. 3*B*).

During the first 18 weeks, 15 patients (8.0%) on placebo, 3 patients (1.6%) on empagliflozin 10 mg, and 5 patients

Table 1—Summary of changes in HbA_{1c}, plasma glucose, insulin dose, and body weight

		Empagliflozin	
	Placebo	10 mg	25 mg
Primary end point			
HbA_{1c} at baseline, % (mmol/mol) (week 18 analysis set)	8.33 ± 0.05 (68 ± 0.5)	8.39 ± 0.05 (68 ± 0.5)	8.29 ± 0.05 (67 ± 0.5)
HbA_{1c} at week 18, % (mmol/mol)	7.84 ± 0.07 (62 ± 0.8)	7.44 ± 0.05 (58 ± 0.5)	7.29 ± 0.06 (56 ± 0.7)
Change from baseline in HbA_{1c}, % (mmol/mol)	−0.50 ± 0.05 (−5.5 ± 0.5)	−0.94 ± 0.05 (−10.3 ± 0.5)	−1.02 ± 0.05 (−11.1 ± 0.5)
Difference vs. placebo (95% CI) (%) [mmol/mol]		−0.44 ± 0.08 (−0.59 to −0.29); [−4.8 ± 0.9 (−6.4 to −3.2)]	−0.52 ± 0.07 (−0.67 to −0.37); [−5.7 ± 0.8 (−7.3 to −4.0)]
P value		<0.001	<0.001
Secondary end points			
Insulin dose at week 52, international units/day	99.5 ± 4.9	90.4 ± 4.0	89.4 ± 4.1
Change from baseline in insulin dose, international units/day	10.2 ± 2.2	1.3 ± 2.1	−1.1 ± 2.1
Difference vs. placebo (95% CI)		−8.8 ± 3.1 (−14.8 to −2.8)	−11.2 ± 3.1 (−17.2 to −5.2)
P value		0.004	<0.001
HbA_{1c} at baseline, % (mmol/mol) (week 52 analysis set)	8.25 ± 0.07 (67 ± 0.8)	8.40 ± 0.07 (68 ± 0.8)	8.37 ± 0.06 (68 ± 0.7)
HbA_{1c} at week 52, % (mmol/mol)	7.48 ± 0.09 (58 ± 1.0)	7.19 ± 0.08 (55 ± 0.9)	7.09 ± 0.08 (54 ± 0.9)
Change from baseline in HbA_{1c}, % (mmol/mol)	−0.81 ± 0.08 (−8.9 ± 0.9)	−1.18 ± 0.08 (−12.9 ± 0.9)	−1.27 ± 0.08 (−13.9 ± 0.9)
Difference vs. placebo (95% CI) (%) [mmol/mol]		−0.38 ± 0.11 (−0.59 to −0.16); [−4.2 ± 1.2 (−6.4 to −1.7)]	−0.46 ± 0.11 (−0.67 to −0.25); [−5.0 ± 1.2 (−7.3 to −2.7)]
P value		<0.001	<0.001
Body weight at week 52, kg	96.66 ± 1.72	94.57 ± 1.47	93.41 ± 1.72
Change from baseline in body weight, kg	0.44 ± 0.36	−1.95 ± 0.36	−2.04 ± 0.36
Difference vs. placebo (95% CI)		−2.39 ± 0.51 (−3.40 to −1.39)	−2.48 ± 0.51 (−3.48 to −1.47)
P value		<0.001	<0.001
Exploratory end points			
Body weight at week 18, kg	95.83 ± 1.27	95.71 ± 1.30	94.37 ± 1.26
Change from baseline in body weight, kg	0.34 ± 0.18	−0.97 ± 0.18	−1.54 ± 0.18
Difference vs. placebo (95% CI)		−1.31 ± 0.26 (−1.82 to −0.80)	−1.88 ± 0.26 (−2.39 to −1.37)
P value		<0.001	<0.001
FPG at baseline, mmol/L	8.41 ± 0.19	8.83 ± 0.20	8.34 ± 0.20
FPG at week 18, mmol/L	8.68 ± 0.22	7.66 ± 0.19	7.09 ± 0.17
Change from baseline in FPG, mmol/L	0.19 ± 0.16	−0.98 ± 0.17	−1.36 ± 0.16
Difference vs. placebo (95% CI)		−1.17 ± 0.23 (−1.62 to −0.71)	−1.55 ± 0.23 (−2.00 to −1.09)
P value		<0.001	<0.001
FPG at week 52, mmol/L	7.95 ± 0.22	7.46 ± 0.22	7.13 ± 0.19
Change from baseline in FPG, mmol/L	−0.63 ± 0.19	−1.32 ± 0.19	−1.43 ± 0.19
Difference vs. placebo (95% CI)		−0.69 ± 0.27 (−1.23 to −0.15)	−0.79 ± 0.27 (−1.33 to −0.26)
P value		0.012	0.004

Data are mean ± SE except for change from baseline values and difference vs. placebo, which are adjusted mean ± SE. HbA_{1c}, FPG, and body weight at week 18 were assessed with ANCOVA in FAS using LOCF. HbA_{1c}, insulin dose, FPG, and body weight at week 52 were assessed with ANCOVA in PPS-completers-52 using LOCF. The FAS is patients treated with study medication who had a baseline HbA_{1c} measurement. The PPS-completers-52 set is patients in the FAS who were on treatment up to day 357 and did not have important protocol violations.

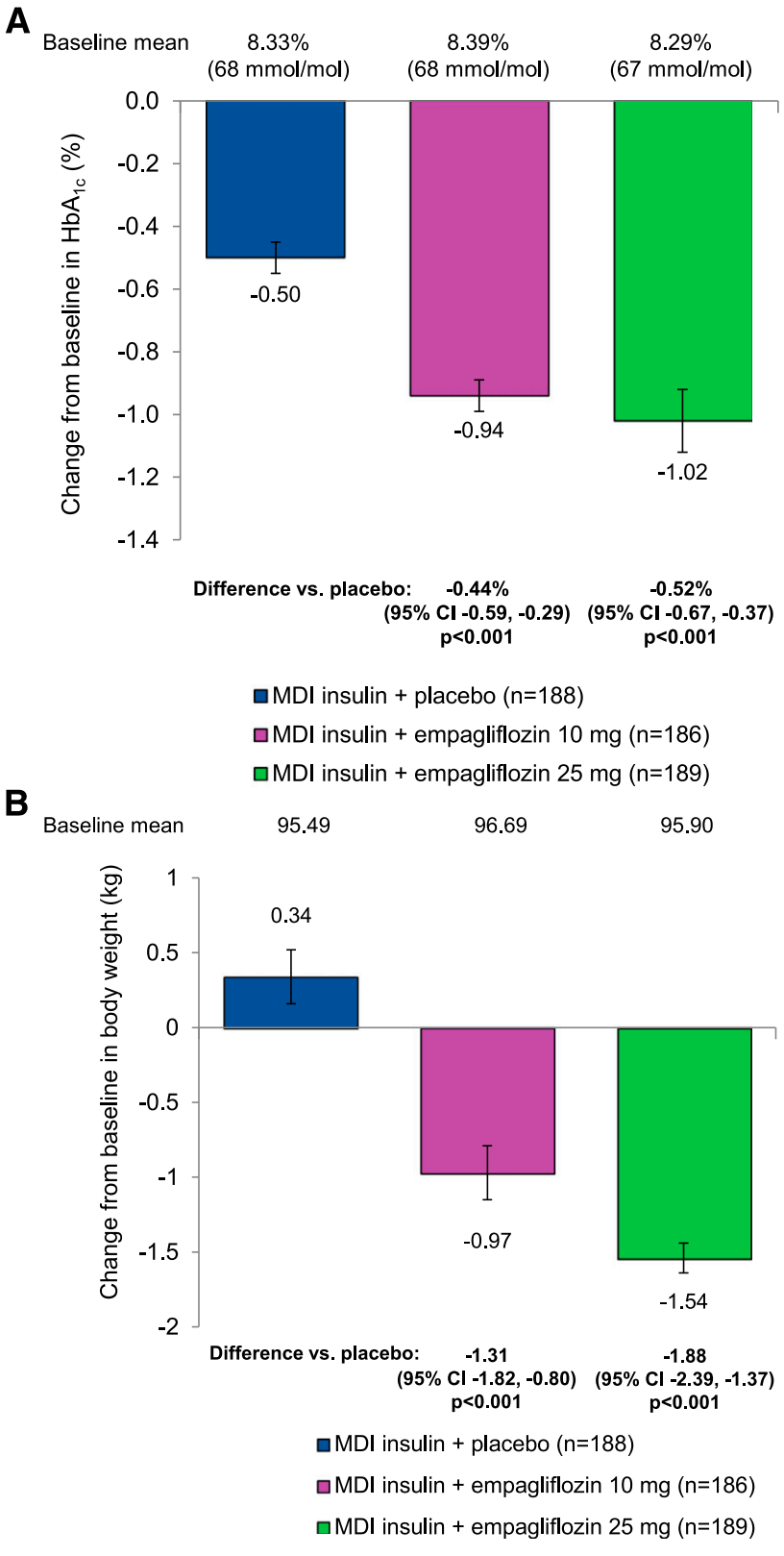

Figure 1—Effect of empagliflozin on efficacy parameters at week 18. *A*: Change from baseline in HbA_{1c} (ANCOVA, FAS, LOCF imputation at week 18). *B*: Change from baseline in body weight (ANCOVA, FAS, LOCF). Data are mean ± SE at baseline and adjusted mean ± SE on treatment. Blue bars represent MDI insulin + placebo, purple bars represent MDI insulin + empagliflozin 10 mg, and green bars represent MDI insulin + empagliflozin 25 mg.

(2.6%) on empagliflozin 25 mg received rescue therapy. The rescue therapy used most often was an increase in insulin dose.

Efficacy: Week 52

Insulin dose was to be adjusted during weeks 19–40 to reach glucose targets and then to remain within 10% of the prescribed dose at week 40 during weeks 41–52. Adjusted mean daily dose of insulin over time is shown in Fig. 2*A*. Adjusted mean HbA_{1c} levels over 52 weeks are shown in Fig. 2*B*. At week 52, adjusted mean ± SE changes from baseline were 10.2 ± 2.2 international units/day with placebo compared with 1.3 ± 2.1 international units/day with empagliflozin 10 mg and −1.1 ± 2.1 international units/day with empagliflozin 25 mg ($P = 0.004$ for empagliflozin 10 mg; $P < 0.001$ for empagliflozin 25 mg) (Table 1, Fig. 2*C*). Corrected for body weight, adjusted mean ± SE changes from baseline were 0.10 ± 0.02 international units/kg with placebo compared with 0.03 ± 0.02 international units/kg with empagliflozin 10 mg (difference of adjusted means vs. placebo, −0.07 international units/kg [95% CI −0.12 to −0.01]; $P = 0.023$) and 0.00 ± 0.02 international units/kg with empagliflozin 25 mg (difference of adjusted means vs. placebo, −0.10 international units/kg [95% CI −0.15 to −0.04]; $P < 0.001$). Mean ± SE changes from baseline in basal insulin dose at week 52 were 9.2 ± 1.9 international units/day for placebo, 3.7 ± 1.5 international units/day for empagliflozin 10 mg, and 2.5 ± 1.5 international units/day for empagliflozin 25 mg. For prandial insulin dose, mean ± SE changes from baseline at week 52 were 0.3 ± 1.3 international units/day for placebo, −1.9 ± 1.0 international units/day for empagliflozin 10 mg, and −3.5 ± 1.3 international units/day for empagliflozin 25 mg. There were no changes from baseline in the number of prandial insulin shots per day in any treatment group.

At week 52, due to the insulin titration in the placebo group, the adjusted mean ± SE change from baseline in HbA_{1c} was −0.81 ± 0.08% (−8.9 ± 0.9 mmol/mol). With much lower insulin titration in the empagliflozin groups, changes were −1.18 ± 0.08% (−12.9 ± 0.9 mmol/mol) with empagliflozin 10 mg and −1.27 ± 0.08% (−13.9 ± 0.9

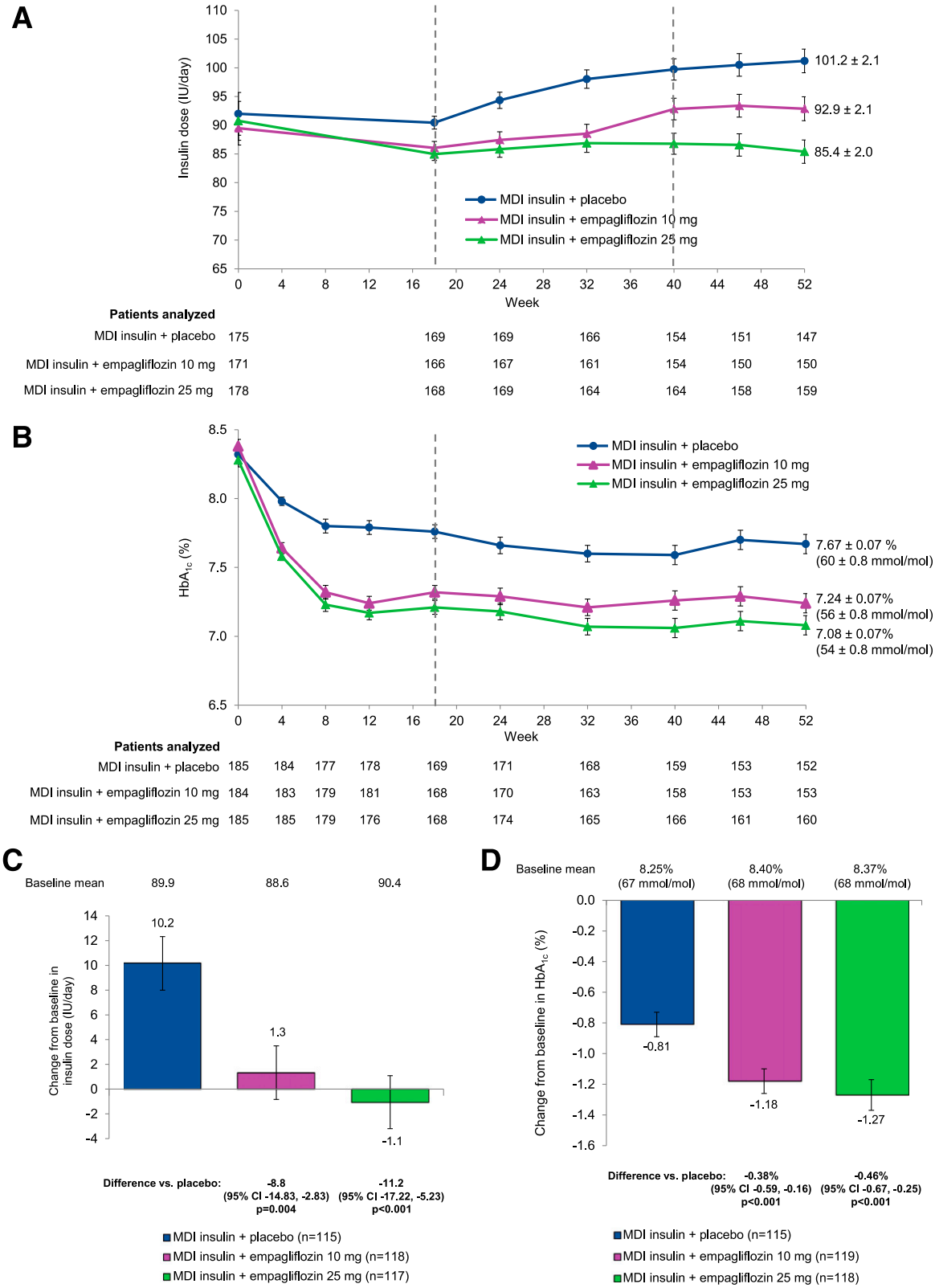

Figure 2—Effect of empagliflozin on efficacy parameters at week 52. *A*: Insulin dose over time (MMRM, FAS, OCs). *B*: HbA_{1c} over time (MMRM, FAS, OCs). *C*: Change from baseline in insulin dose (ANCOVA, PPS-completers-52, LOCF imputation). *D*: Change from baseline in HbA_{1c} (ANCOVA, PPS-completers-52, LOCF). *E*: Percentage of patients with HbA_{1c} ≥7% (≥53 mmol/mol) at baseline who reached HbA_{1c} <7% at week 52 (logistic regression, FAS, noncompleters considered failures). *F*: Change from baseline in body weight (ANCOVA, PPS-completers-52, LOCF). Data are mean ± SE at baseline and adjusted mean ± SE on treatment. PPS-completers-52 set is patients who were on treatment up to day 357 and did not have important protocol violations. Blue circles/bars represent MDI insulin + placebo, purple triangles/bars represent MDI insulin + empagliflozin 10 mg, and green triangles/bars represent MDI insulin + empagliflozin 25 mg. IU, international units.

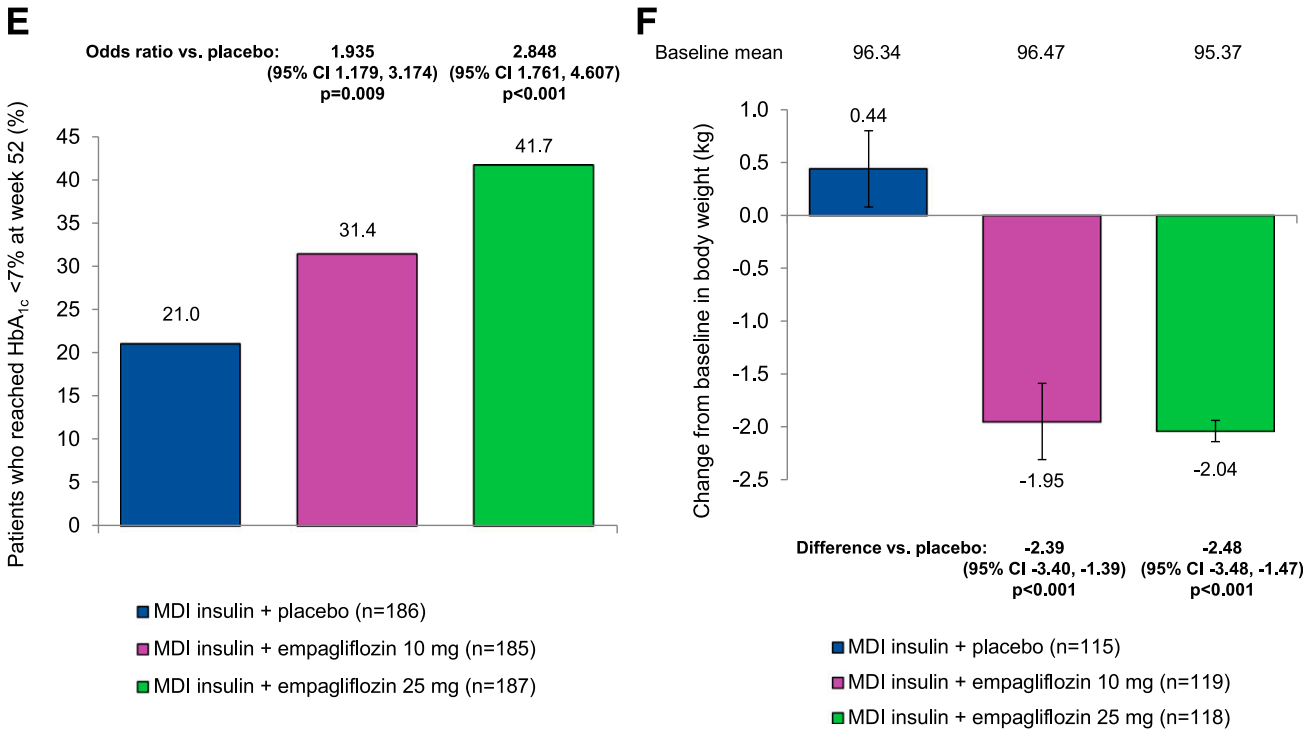

Figure 2—*Continued.*

mmol/mol) with empagliflozin 25 mg ($P < 0.001$ for both) (Table 1, Fig. 2*D*). Of note, a significant proportion of patients with HbA_{1c} ≥7.0% (≥53 mmol/mol) at baseline reached HbA_{1c} <7.0% with empagliflozin 10 mg (31.4%) and empagliflozin 25 mg (41.7%; $P < 0.01$ for odds ratio vs. placebo [21.0%]) (Fig. 2*E*).

Adjusted mean ± SE changes from baseline in FPG at week 52 were −0.63 ± 0.19 mmol/L with placebo compared with −1.32 ± 0.19 mmol/L with empagliflozin 10 mg ($P = 0.012$) and −1.43 ± 0.19 mmol/L with empagliflozin 25 mg ($P = 0.004$) (Table 1, Supplementary Fig. 2*B*).

Treatment with empagliflozin significantly reduced body weight at week 52. Adjusted mean ± SE changes from baseline were 0.44 ± 0.36 kg with placebo compared with −1.95 ± 0.36 kg with empagliflozin 10 mg and −2.04 ± 0.36 kg with empagliflozin 25 mg (differences of adjusted means vs. placebo were −2.39 kg [95% CI −3.40 to −1.39] for empagliflozin 10 mg and −2.48 kg [95% CI −3.48 to −1.47] for empagliflozin 25 mg; $P <$ 0.001 for both) (Table 1, Fig. 2*F*).

Changes from baseline in SBP with both doses of empagliflozin and in DBP with empagliflozin 10 mg did not reach significance versus placebo at week 52 (Supplementary Table 2, Supplementary Fig. 3*C* and *D*). Mean ± SE change from baseline in DBP was greater with empagliflozin 25 mg than placebo (−2.5 ± 0.6 vs. −0.5 ± 0.6 mmHg; $P = 0.035$) at week 52 (Supplementary Table 2, Supplementary Fig. 3*D*). No clinically meaningful changes in pulse rate were noted.

Safety

Data on AEs are shown in Table 2. Over the 52-week treatment period, the proportions of patients with ≥1 AE, ≥1 serious AE, or ≥1 AE leading to discontinuation were similar across the treatment groups, with ∼90% of patients reporting only mild or moderate events. One death occurred (metastatic lung cancer in a patient in the empagliflozin 25 mg group).

The proportion of patients with confirmed hypoglycemic AEs up to week 18 was slightly higher in the empagliflozin 10 mg group (74 patients [39.8%]) and the empagliflozin 25 mg group (78 patients [41.3%]) compared with the placebo group (70 patients [37.2%]). However, only one patient in each of the three treatment groups had severe hypoglycemic AEs (requiring assistance). Over the full 52-week treatment period, including the treat-to-target period, the proportion of patients with confirmed hypoglycemic AEs was similar in all treatment groups (placebo, 109 patients [58.0%]; empagliflozin 10 mg, 95 patients [51.1%]; empagliflozin 25 mg, 109 patients [57.7%]). Three patients each in the placebo and empagliflozin 10 mg groups and one in the empagliflozin 25 mg group had severe hypoglycemia (requiring assistance).

Over the 52-week treatment period, events consistent with urinary tract infection were reported in similar proportions of patients on placebo (15.4%), empagliflozin 10 mg (15.6%), and empagliflozin 25 mg (15.3%). More female patients (24.8–27.0%) than male patients (0–5.2%) reported these events across all treatment groups. The majority of patients who reported any events consistent with urinary tract infection reported only mild events. One patient (on empagliflozin 25 mg) reported a severe event, one patient (on empagliflozin 25 mg) reported ≥1 event that required hospitalization, and no urinary tract infection events led to study discontinuation. Events consistent with genital infections were reported in more patients in the empagliflozin 10 mg (4.3%) and empagliflozin 25 mg (9.5%) groups compared with the placebo group (1.6%). These events were reported in a greater proportion of

Table 2—Summary of AEs

	Placebo (*n* = 188)	Empagliflozin 10 mg (*n* = 186)	Empagliflozin 25 mg (*n* = 189)
One or more AEs	169 (89.9)	160 (86.0)	160 (84.7)
One or more drug-related* AEs	64 (34.0)	56 (30.1)	76 (40.2)
AEs leading to discontinuation	9 (4.8)	10 (5.4)	9 (4.8)
One or more serious AEs	22 (11.7)	20 (10.8)	22 (11.6)
Deaths	0 (0)	0 (0)	1 (0.5)
AEs with frequency ≥5% in any group (by preferred term)			
Hypoglycemia	111 (59.0)	97 (52.2)	110 (58.2)
Nasopharyngitis	40 (21.3)	34 (18.3)	27 (14.3)
Urinary tract infection	23 (12.2)	24 (12.9)	24 (12.7)
Diarrhea	17 (9.0)	12 (6.5)	18 (9.5)
Back pain	14 (7.4)	12 (6.5)	15 (7.9)
Arthralgia	10 (5.3)	18 (9.7)	11 (5.8)
Influenza	12 (6.4)	7 (3.8)	14 (7.4)
Bronchitis	12 (6.4)	10 (5.4)	8 (4.2)
Headache	9 (4.8)	8 (4.3)	11 (5.8)
Hyperglycemia	14 (7.4)	6 (3.2)	8 (4.2)
Hypertension	10 (5.3)	9 (4.8)	7 (3.7)
Dizziness	2 (1.1)	5 (2.7)	13 (6.9)
Gastroenteritis	10 (5.3)	8 (4.3)	1 (0.5)
Special interest categories			
Confirmed hypoglycemic AEs†	109 (58.0)	95 (51.1)	109 (57.7)
Severe hypoglycemic AEs‡	3 (1.6)	3 (1.6)	1 (0.5)
Events consistent with urinary tract infection§	29 (15.4)	29 (15.6)	29 (15.3)
Male	0 (0)	5 (5.2)	3 (3.6)
Female	29 (25.7)	24 (27.0)	26 (24.8)
Acute pyelonephritis or urosepsis	0 (0)	0 (0)	0 (0)
Events consistent with genital infection∏	3 (1.6)	8 (4.3)	18 (9.5)
Male	1 (1.3)	1 (1.0)	7 (8.3)
Female	2 (1.8)	7 (7.9)	11 (10.5)

Data are *n* (%) for patients treated with ≥1 dose of trial medication. *As assessed by the investigator. †AEs consistent with hypoglycemia and with plasma glucose ≤70 mg/dL and/or requiring assistance. ‡AEs consistent with hypoglycemia and with plasma glucose ≤70 mg/dL and requiring assistance. §Reports of urinary tract infection were based on 70 preferred terms. ∏Reports of genital infection were based on 89 preferred terms.

female patients on empagliflozin 10 mg (7/89 [7.9%]) or empagliflozin 25 mg (11/105 [10.5%]) than on placebo (2/118 [1.8%]) and in a greater proportion of male patients on empagliflozin 25 mg (7/84 [8.3%]) than on empagliflozin 10 mg (1/97 [1.0%]) or placebo (1/75 [1.3%]). All such events were mild or moderate in intensity, only one patient (on empagliflozin 25 mg) experienced an event that led to discontinuation, and no patients reported events that required or prolonged hospitalization.

Changes in laboratory parameters are shown in Supplementary Table 3. There were small decreases from baseline in uric acid and small increases from baseline in hematocrit (~4%) with empagliflozin. Electrolyte levels were unchanged across treatment groups. There were small decreases from baseline to end of treatment in mean eGFR in all treatment groups, which returned to baseline levels at follow-up in the empagliflozin groups. No major differences between placebo and empagliflozin in mean changes from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides were noted.

CONCLUSIONS

This is the first dedicated trial to determine the efficacy and safety of an SGLT2 inhibitor in the difficult-to-treat population of obese, insulin-resistant patients with insufficient glycemic control despite high-dose MDI insulin. Compared with insulin titrations alone, which resulted in HbA_{1c} reductions to 7.5% (58 mmol/mol), the addition of empagliflozin 10 mg and empagliflozin 25 mg to titrated MDI insulin improved glycemic control further, despite lower insulin doses, to achieve HbA_{1c} levels of 7.2 and 7.1% (55 and 54 mmol/mol), respectively, with no increase in the risk of hypoglycemia and with weight loss.

The use of insulin in patients with T2DM is associated with a high risk of hypoglycemic events and weight gain, complicating the management of hyperglycemia (14). Fear of hypoglycemia and weight gain decrease adherence to medication (15,16), while insulin-induced weight gain in patients with T2DM is associated with worsening of insulin resistance (1), resulting in a vicious cycle. This study investigating the effect of empagliflozin as an add-on to MDI insulin is unique in its study design, as it comprised three distinct insulin dosing periods. In a stable MDI insulin period during the first 18 weeks, empagliflozin resulted in significant HbA_{1c} reduction and weight loss compared with placebo, with a slightly increased frequency of mild hypoglycemic events but no increase in severe hypoglycemic events. An increased frequency of hypoglycemia has previously been reported when antidiabetes agents with a low risk of hypoglycemia are added to insulin (17,18). Of note, over the full 52-week treatment period, including the treat-to-target period, the proportion of patients with confirmed hypoglycemic AEs was similar in all treatment groups. This might be explained by differences in insulin titration in the empagliflozin and placebo arms due to the insulin-independent mechanism of action of empagliflozin (13); the incomplete inhibition of renal glucose reabsorption by empagliflozin (19); a diminished effect of SGLT2 inhibition at low glucose levels due to physiological decline in glomerular filtration rate (due to sympathetic nervous system activation) (20); a compensatory increase in hepatic gluconeogenesis (21); or a combination of these factors.

The change from baseline in HbA_{1c} in the placebo group at week 18 was more pronounced than previously observed in studies with empagliflozin. We may speculate that changes in diet and lifestyle due to participation in a dedicated MDI insulin trial may itself have resulted in improved glycemic control in this obese, insulin-resistant population, reinforcing the general paradigm that pharmacological treatment of diabetes

has to be accompanied by diet and lifestyle intervention.

Empagliflozin was well tolerated when used in combination with MDI insulin with or without metformin for 52 weeks. Empagliflozin was not associated with a higher rate of events consistent with urinary tract infections but was associated with an increased risk of events consistent with genital infection, as has been observed in other studies of SGLT2 inhibitors (22). However, no events consistent with genital infection were severe, and such events led to premature discontinuation in only one patient. Small decreases in eGFR during treatment with empagliflozin likely reflected hemodynamic changes, as eGFR had returned to baseline levels 4 weeks after treatment discontinuation, consistent with the results of another phase III study that examined the effect of empagliflozin on renal function over time (23).

Limitations of this trial include that insulin titration was at the investigator's discretion based on prespecified treatment goals and was not defined or enforced by an independent insulin titration monitoring committee. Therefore, the full effect of empagliflozin on titrated insulin doses cannot be fully assessed. Furthermore, the conclusions from this study are limited to the population studied and are not applicable to the general population of patients with T2DM.

In conclusion, in obese patients with T2DM and inadequate glycemic control despite MDI insulin, empagliflozin 10 mg and empagliflozin 25 mg once daily for 52 weeks improved glycemic control and reduced body weight without increasing the risk of hypoglycemia and with lower insulin requirements. This suggests that empagliflozin may provide a new treatment option for this challenging-to-treat patient population.

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