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ORIGINAL ARTICLE

Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial

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Aims: To investigate the efficacy and tolerability of empagliflozin added to basal insulin-treated type 2 diabetes.

Methods: Patients inadequately controlled [glycated haemoglobin (HbA1c) >7 to ≤10% (>53 to ≤86 mmol/mol)] on basal insulin (glargine, detemir, NPH) were randomized to empagliflozin 10 mg (n = 169), empagliflozin 25 mg (n = 155) or placebo (n = 170) for 78 weeks. The baseline characteristics were balanced among the groups [mean HbA1c 8.2% (67 mmol/mol), BMI 32.2 kg/m^2]. The basal insulin dose was to remain constant for 18 weeks, then could be adjusted at investigator's discretion. The primary endpoint was change from baseline in HbA1c at week 18. Key secondary endpoints were changes from baseline in HbA1c and insulin dose at week 78.

Results: At week 18, the adjusted mean ± standard error changes from baseline in HbA1c were 0.0 ± 0.1% (−0.1 ± 0.8 mmol/mol) for placebo, compared with −0.6 ± 0.1% (−6.2 ± 0.8 mmol/mol) and −0.7 ± 0.1% (−7.8 ± 0.8 mmol/mol) for empagliflozin 10 and 25 mg, respectively (both $p < 0.001$). At week 78, empagliflozin 10 and 25 mg significantly reduced HbA1c, insulin dose and weight vs placebo (all $p < 0.01$), and empagliflozin 10 mg significantly reduced systolic blood pressure vs placebo ($p = 0.004$). Similar percentages of patients had confirmed hypoglycaemia in all groups (35–36%). Events consistent with urinary tract infection were reported in 9, 15 and 12% of patients on placebo, empagliflozin 10 and 25 mg, and events consistent with genital infection were reported in 2, 8 and 5%, respectively.

Conclusions: Empagliflozin for 78 weeks added to basal insulin improved glycaemic control and reduced weight with a similar risk of hypoglycaemia to placebo.

Keywords: empagliflozin, SGLT2 inhibitor, type 2 diabetes

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Introduction

Guidelines for the management of type 2 diabetes recommend early initiation of basal insulin in patients who fail to achieve glycaemic targets with oral agents [1]. Clinical trials have shown that the addition of basal insulin to oral agents in patients with inadequate glycaemic control enables 50–60% of patients to achieve glycaemic targets when basal insulin is consistently titrated [2–5]; however, initiation of insulin therapy is often delayed and patients may have glycated haemoglobin (HbA1c) levels >8% for nearly 5 years before insulin is introduced [6]. Even when insulin is initiated, the insulin regimen may not be optimized, resulting in patients failing to achieve glycaemic control [7]. Delays in initiating or optimizing insulin therapy arise from a number of concerns among healthcare providers and patients, including the perception that inflexible insulin regimens are restrictive to daily life, as well as the fear of hypoglycaemia and weight gain [8–10]. There remains an unmet need for oral antidiabetes agents that can be added to insulin therapy to facilitate further improvements in glycaemic control without causing hypoglycaemia or weight gain.

Empagliflozin is a potent, selective inhibitor of the sodium glucose cotransporter 2 (SGLT2) [11] that reduces renal glucose reabsorption, leading to increased urinary glucose excretion and a reduction in hyperglycaemia [12]. In phase III trials, empagliflozin given for 24 weeks as monotherapy, as add-on to pioglitazone alone or with metformin, or as add-on to metformin alone or with sulphonylurea reduced HbA1c, weight and blood pressure in patients with type 2 diabetes [13–16]. Furthermore, empagliflozin was well tolerated, with a low risk of hypoglycaemia but with an increased frequency of mild genitourinary infections typical of the class [13–16]. The mechanism of action of SGLT2 inhibitors is independent of insulin, making these a promising class of agents to be combined with

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exogenous insulin [12]; in addition to improving glucose control, SGLT2 inhibitors may reduce insulin dose requirements and mitigate insulin-induced weight gain.

The aim of the present study was to evaluate the efficacy, safety and tolerability of add-on therapy with empagliflozin (10 and 25 mg once daily) versus placebo over 78 weeks in patients with type 2 diabetes inadequately controlled on basal insulin, with or without metformin and/or sulphonylureas.

Materials and Methods

Study Design

This was a randomized, placebo-controlled, double-blind phase IIb study, conducted from November 2009 to May 2012 in 97 centres in seven countries (Denmark, France, Ireland, Korea, Portugal, UK and USA). The clinical trial protocol was approved by the Institutional Review Boards and Independent Ethics Committees and Competent Authorities of the participating centres, and the trial complied with the Declaration of Helsinki in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice. The trial was registered with ClinicalTrials.gov (NCT01011868). All patients provided written informed consent.

Inclusion and Exclusion Criteria

The study enrolled adults with a body mass index (BMI) ≤45 kg/m^2 and inadequately controlled type 2 diabetes [HbA1c >7 to ≤10% (>53 to ≤86 mmol/mol) at screening], despite treatment with basal glargine or detemir insulin (≥20 IU/day) or NPH insulin (≥14 IU/day; at a dose unchanged by >10% of baseline value for ≥12 weeks before randomization), with or without metformin and/or sulphonylurea use (unchanged for ≥12 weeks prior to randomization).

Exclusion criteria included: uncontrolled hyperglycaemia [glucose level >13.3 mmol/l (>240 mg/dl) after an overnight fast or >22.2 mmol/l (>400 mg/dl) from a random assessment during placebo run-in]; frequent hypoglycaemic events on basal insulin therapy (in the opinion of the investigator); myocardial infarction, stroke or transient ischaemic attack <3 months before consent; estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2; bariatric surgery; investigational drug intake within 2 months of consent; and treatment with anti-obesity drugs, any oral antidiabetes medication (other than metformin or sulphonylurea), chronic short-acting insulin or glucagon-like peptide-1 receptor agonists within 3 months of consent. Further exclusion criteria are given in the supplementary methods section (File S1).

Treatment and Interventions

After a 2-week open-label placebo run-in period, eligible patients were randomized (1 : 1 : 1) to receive once-daily empagliflozin 10 mg, empagliflozin 25 mg or placebo, as add-on to basal insulin, with or without metformin and/or sulphonylureas, for 78 weeks. Randomization was performed using a third-party interactive voice and web response system, and was stratified by HbA1c at screening [<8.5% (<69 mmol/mol), ≥8.5% (≥69 mmol/mol)] and centre. For the first 18 weeks, patients were to remain on a fixed dose of basal insulin; during the subsequent 60 weeks, the insulin dose was to be adjusted at the discretion of the investigator for any confirmed fasting plasma glucose (FPG) level >6.1 mmol/l (>110 mg/dl). Metformin and/or sulphonylurea were to remain unchanged. Study visits were scheduled at screening; at the start of the placebo run-in period; and at weeks 0, 6, 12, 18, 30, 42, 54, 66 and 78 of treatment. A follow-up visit was made at week 82.

Rescue therapy could be initiated during treatment if a patient had: a confirmed glucose level >22.2 mmol/l (>400 mg/dl) from a randomly performed measurement; or between weeks 1 and 12, a confirmed glucose level >13.3 mmol/l (>240 mg/dl) after an overnight fast; or between weeks 12 and 18, a confirmed glucose level >11.1 mmol/l (>200 mg/dl) after an overnight fast; or between weeks 18 and 78, a confirmed glucose level >10.0 mmol/l (>180 mg/dl) after an overnight fast or HbA1c >8.0% (>64 mmol/mol). Changes in dose of metformin or sulphonylureas for ≥7 days or addition of a new antidiabetes agent for ≥7 days were considered as rescue therapy. Changes in basal insulin use were not considered as rescue therapy for the efficacy analyses after week 18. Further details of rescue therapy in the first 18 weeks are given in the supplementary methods (File S1). In cases of hypoglycaemia, the dose of background or rescue medication could be reduced. Where hyper- or hypoglycaemia could not be controlled, the subject discontinued participation in the trial.

Endpoints and Assessments

The primary endpoint was change from baseline in HbA1c at week 18. Key secondary endpoints were changes from baseline to week 78 in basal insulin dose and HbA1c. Additional secondary endpoints included: changes from baseline to weeks 18 and 78 in FPG and body weight, and percentage of patients with HbA1c ≥7% (≥53 mmol/mol) at baseline who had HbA1c <7% (<53 mmol/mol) at weeks 18 and 78. Exploratory endpoints included changes from baseline to weeks 18 and 78 in systolic (SBP) and diastolic blood pressure (DBP). Blood pressure measurements were taken after 5 mins of rest in the seated position; recordings taken using the same instrument on the same arm.

Safety endpoints included vital signs, clinical laboratory and lipid variables and adverse events (AEs; preferred terms coded according to the Medical Dictionary for Drug Regulatory Activities version 15.0). AEs included all events with an onset after the first dose and up to 7 days after the last dose of study medication. Confirmed hypoglycaemic AEs [plasma glucose ≤3.9 mmol/l (≤70 mg/dl) and/or requiring assistance], and events consistent with urinary tract and genital infections (identified using prospectively defined search categories based on 70 and 89 preferred terms, respectively) were assessed.

Statistical Analysis

The primary efficacy analysis was performed on completers in the full analysis set (FAS; randomized patients treated with ≥1 dose of study drug and who had a baseline HbA1c value) at week 18 (FAS-18 completers; patients in the FAS who did not discontinue the trial before week 18, had a treatment

duration of ≥119 days, and had an on-treatment HbA1c value available in that visit window). Key secondary endpoints were analysed on the FAS-78 completers (patients in the FAS who did not discontinue before week 78, had a treatment duration of ≥532 days, and had an on-treatment HbA1c value available at day 532 or later). Efficacy analyses of other endpoints were performed on the FAS. Safety analyses were performed on the treated set (patients treated with ≥1 dose of study drug). Changes in eGFR, haematocrit and lipid variables were also assessed in the follow-up set (patients in the FAS with a follow-up visit performed >2 weeks after the study drug stop date).

The primary endpoint was assessed using an analysis of covariance model, with treatment and region as fixed effects and baseline HbA1c as a linear covariate. Secondary endpoints and continuous exploratory endpoints were analysed using the statistical model described above, with the baseline value for the endpoint in question as an additional linear covariate. Values after initiation of rescue therapy were set to missing and imputed using the last observation carried forward (LOCF) approach. Changes over time in HbA1c, insulin dose, FPG and body weight were analysed using restricted maximum likelihood-based mixed model repeated measures (MMRM). Categorical response in HbA1c was analysed by logistic regression. Safety analyses were descriptive. Further details on statistical analysis, including sample size calculation, are given in the supplementary methods section (File S1).

Results

Patients

A total of 494 patients were randomized to placebo (n = 170), empagliflozin 10 mg (n = 169), or empagliflozin 25 mg (n = 155), comprising the FAS (Figure S1). Of these, 429 (87%) patients completed 18 weeks' treatment, and 360 (73%) patients completed 78 weeks' treatment. Baseline characteristics were balanced across groups (Table S1). The patients' mean ± standard deviation (s.d.) age was 58.8 ± 9.9 years, and 89% had been diagnosed with type 2 diabetes for >5 years. At baseline, the mean ± s.d. HbA1c was 8.2 ± 0.8% (67 ± 9.0 mmol/mol), and 36% of patients had an HbA1c level ≥8.5% (>69 mmol/mol). At baseline, 40% of patients were on background basal insulin plus metformin, 39% were on background basal insulin plus metformin and sulphonylurea, 10% were on basal insulin plus sulphonylurea and 10% were on basal insulin only. Glargine was taken by 58% of patients, 19% were on insulin detemir and 14% were on NPH insulin (Table S1).

Efficacy: Week 18

During the first 18 weeks of treatment, patients were to remain on a fixed dose of basal insulin. At week 18, adjusted mean ± standard error (s.e.) changes from baseline in HbA1c were 0 ± 0.1% (−0.1 ± 0.8 mmol/mol) with placebo compared with −0.6 ± 0.1% (−6.2 ± 0.8 mmol/mol) with empagliflozin 10 mg and −0.7 ± 0.1% (−7.8 ± 0.8 mmol/mol) with empagliflozin 25 mg (both p < 0.001; Figure 1A; Table 1). In patients with HbA1c ≥7.0% (≥53 mmol/mol) at baseline, a greater proportion reached HbA1c <7.0% (<53 mmol/mol) with empagliflozin 10 mg (18.0%) or 25 mg (19.5%) compared with placebo (5.5%) and the odds ratios versus placebo were 4.1 [95% confidence interval (CI) 1.8, 9.1] for empagliflozin 10 mg and 4.6 (95% CI 2.1, 10.3) for empagliflozin 25 mg; (both p < 0.001; Table S2).

Adjusted mean ± s.e. changes from baseline in FPG were 0.6 ± 0.2 mmol/l (10.4 ± 3.1 mg/dl) with placebo compared with −1.0 ± 0.2 mmol/l (−17.8 ± 3.2 mg/dl) with empagliflozin 10 mg and −1.1 ± 0.2 mmol/l (−19.1 ± 3.3 mg/dl) with empagliflozin 25 mg (both p < 0.001; Figure 1B; Table 1).

Body weight remained unchanged from baseline with placebo (0.0 ± 0.6 kg) compared with a decrease with empagliflozin 10 mg (−1.7 ± 0.6 kg; p = 0.035) and empagliflozin 25 mg (−0.9 ± 0.6 kg; p = 0.293) (Figure 1C; Table 1).

Adjusted mean ± s.e. changes from baseline in SBP were −0.3 ± 0.9 mmHg with placebo compared with −3.7 ± 0.9 mmHg with empagliflozin 10 mg (p = 0.011) and −3.3 ± 1.0 mmHg with empagliflozin 25 mg (p = 0.027; Figure 1D; Table S3). Adjusted mean ± s.e. changes from baseline in DBP were −0.4 ± 0.6 mmHg with placebo compared with −3.6 ± 0.6 mmHg with empagliflozin 10 mg (p < 0.001). The change from baseline in DBP with empagliflozin 25 mg did not reach significance versus placebo (Figure 1E; Table S3).

Efficacy: Week 78

After week 18, the insulin dose was to be adjusted at the discretion of the investigator for any confirmed FPG level >6.1 mmol/l (>110 mg/dl). Adjusted mean HbA1c levels over the 78-week study are shown in Figure 2A. Adjusted mean changes from baseline were 0 ± 0.1% (−0.2 ± 1.0 mmol/mol) with placebo compared with −0.5 ± 0.1% (−5.2 ± 0.9 mmol/mol) with empagliflozin 10 mg and −0.6 ± 0.1% (−7.0 ± 1.0 mmol/mol) with empagliflozin 25 mg (both p < 0.001; Figure 2B; Table 1). The proportion of patients with HbA1c ≥7.0% at baseline who reached HbA1c <7.0% at week 78 was significantly greater with empagliflozin 25 mg (17.5%) compared with placebo (6.7%); odds ratio 3.2 [95% CI 1.5, 6.9; p = 0.002 (Table S2)].

Figure 2C shows FPG values over time. Adjusted mean ± s.e. changes were 0.2 ± 0.2 mmol/l (2.8 ± 3.2 mg/dl) with placebo compared with −0.6 ± 0.2 mmol/l (−10.1 ± 3.2 mg/dl) with empagliflozin 10 mg (p = 0.005) and −0.8 ± 0.2 mmol/l (−15.2 ± 3.4 mg/dl) with empagliflozin 25 mg (p < 0.001; Figure 2D; Table 1). Sensitivity analysis using an MMRM model showed significantly greater reductions in FPG at week 78 with empagliflozin 25 mg compared with placebo, but not with empagliflozin 10 mg.

Basal insulin doses over time are shown in Figure 2E. Adjusted mean ± s.e. changes from baseline were 5.5 ± 1.6 IU with placebo compared with −1.2 ± 1.5 IU with empagliflozin 10 mg (p = 0.002) and −0.5 ± 1.6 IU with empagliflozin 25 mg (p = 0.009; Figure 2F; Table 1). Body weight over time is shown in Figure 2G. Adjusted mean ± s.e. changes were 0.7 ± 0.5 kg with placebo compared with sustained weight loss of −2.2 ± 0.5 kg with empagliflozin 10 mg and −2.0 ± 0.5 kg with empagliflozin 25 mg (both p < 0.001; Figure 2H; Table 1).

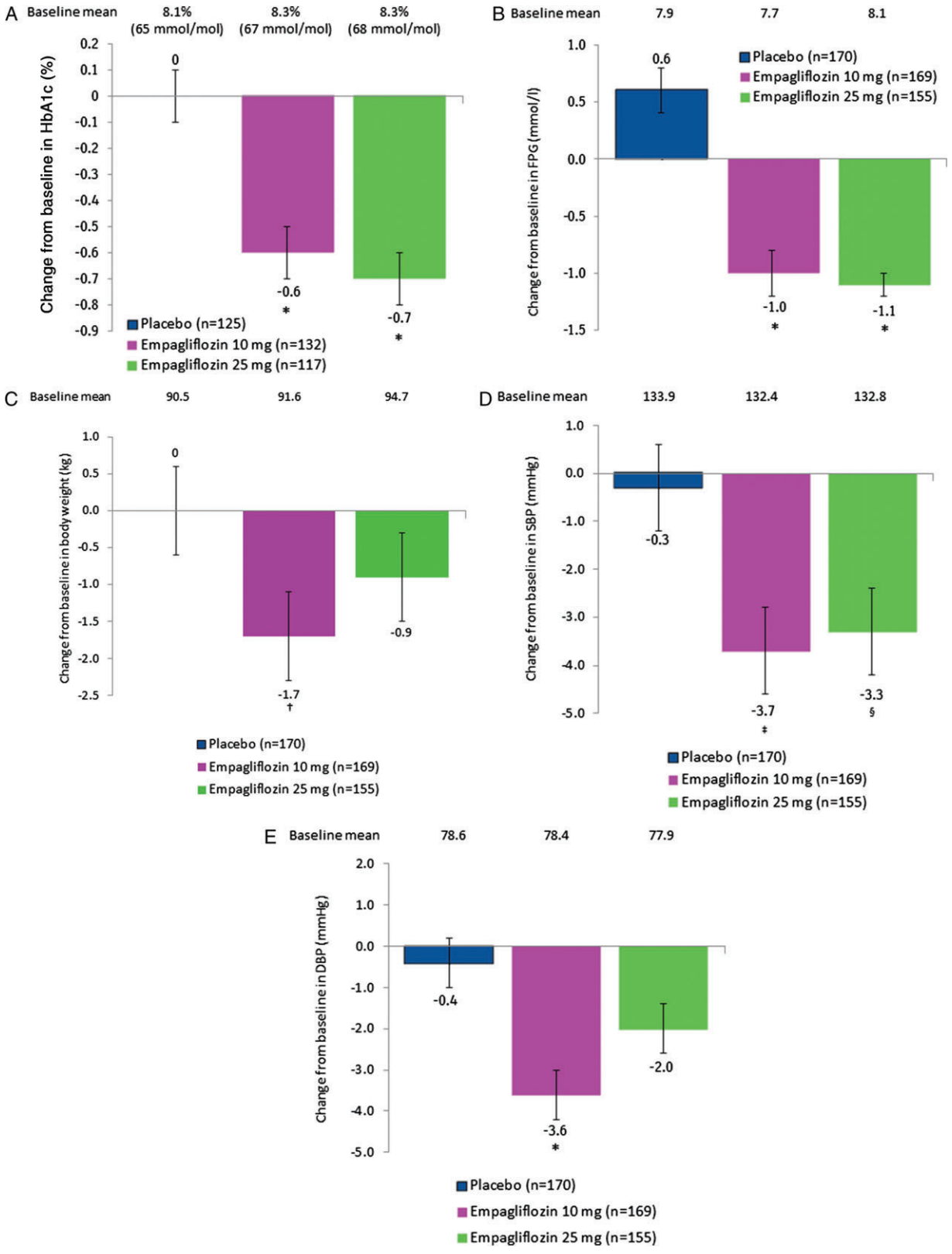


Figure 1. Effect of empagliflozin on efficacy parameters at week 18. (A) change from baseline in glycated haemoglobin [HbA1c; analyis of covariance (ANCOVA), full analysis set (FAS) week 18 completers, last observation carried forward (LOCF) imputation]; (B) change from baseline in fasting plasma glucose (FPG; ANCOVA, FAS, LOCF); (C) change from baseline in body weight (ANCOVA, FAS, LOCF); (D) change from baseline in systolic blood pressure (SBP; ANCOVA, FAS, LOCF); (E) change from baseline in diastolic blood pressure (DBP; ANCOVA, FAS, LOCF). Data are adjusted mean ± standard error. $^{*}p < 0.001$ vs placebo; $^{\dagger}p = 0.035$ vs placebo; $^{\ddagger}p = 0.011$ vs placebo; $^{\S}p = 0.027$ vs placebo.

Table 1. Summary of changes in glycated haemoglobin, plasma glucose, insulin dose and body weight at weeks 18 and 78.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Primary endpoint			
HbA1c at baseline			
%	8.1 ± 0.1	8.3 ± 0.1	8.3 ± 0.1
mmol/mol	65 ± 0.8	67 ± 0.8	68 ± 0.9
HbA1c at week 18			
%	8.1 ± 0.1	7.7 ± 0.1	7.6 ± 0.1
mmol/mol	65 ± 1.1	60 ± 1.0	59 ± 0.9
Change from baseline in HbA1c			
%	0.0 ± 0.1	−0.6 ± 0.1	−0.7 ± 0.1
mmol/mol	−0.1 ± 0.8	−6.2 ± 0.8	−7.8 ± 0.8
Difference vs placebo (95% CI)			
%	—	−0.6 ± 0.1 (−0.8, −0.4)	−0.7 ± 0.1 (−0.9, −0.5)
mmol/mol		−6.1 ± 1.1 (−8.2, −3.9)	−7.7 ± 1.1 (−9.8, −5.5)
p value		<0.001	<0.001
Key secondary endpoints			
HbA1c at baseline			
%	8.1 ± 0.1	8.3 ± 0.1	8.3 ± 0.1
mmol/mol	65 ± 0.8	67 ± 0.8	67 ± 0.9
HbA1c at week 78			
%	8.1 ± 0.1	7.8 ± 0.1	7.6 ± 0.1
mmol/mol	65 ± 1.2	61 ± 0.9	60 ± 1.0
Change from baseline in HbA1c			
%	0.0 ± 0.1	−0.5 ± 0.1	−0.6 ± 0.1
mmol/mol	−0.2 ± 1.0	−5.2 ± 0.9	−7.0 ± 1.0
Difference vs placebo (95% CI)			
%	—	−0.5 ± 0.1 (−0.7, −0.2)	−0.6 ± 0.1 (−0.9, −0.4)
mmol/mol		−5.0 ± 1.3 (−7.7, −2.5)	−6.8 ± 1.3 (−9.5, −4.2)
p value		<0.001	<0.001
Insulin dose at baseline, IU	47.8 ± 3.1	45.1 ± 2.6	48.4 ± 2.8
Insulin dose at week 78, IU	52.6 ± 3.0	44.4 ± 2.3	48.0 ± 2.8
Change from baseline in insulin dose, IU	5.5 ± 1.6	−1.2 ± 1.5	−0.5 ± 1.6
Difference vs placebo (95% CI)	—	−6.7 ± 2.2 (−10.9, −2.4)	−5.9 ± 2.3 (−10.4, −1.5)
p value		0.002	0.009
Secondary endpoints			
FPG at baseline, mmol/l	7.9 ± 0.2	7.7 ± 0.2	8.1 ± 0.2
FPG at week 18, mmol/l	8.4 ± 0.3	6.8 ± 0.2	6.9 ± 0.2
Change from baseline in FPG, mmol/l	0.6 ± 0.2	−1.0 ± 0.2	−1.1 ± 0.2
Difference vs placebo (95% CI)	—	−1.6 ± 0.2 (−2.1, −1.1)	−1.6 ± 0.3 (−2.1, −1.1)
p value		<0.001	<0.001
FPG at week 78, mmol/l	8.0 ± 0.2	7.2 ± 0.2	7.1 ± 0.2
Change from baseline in FPG, mmol/l	0.2 ± 0.2	−0.6 ± 0.2	−0.8 ± 0.2
Difference vs placebo (95% CI)	—	−0.7 ± 0.3 (−1.2, −0.2)	−1.0 ± 0.3 (−1.5, −0.5)
p value		0.005	<0.001
Body weight at baseline, kg	90.5 ± 1.7	91.6 ± 1.5	94.7 ± 1.7
Body weight at week 18, kg	90.4 ± 1.8	89.9 ± 1.5	93.9 ± 2.1
Change from baseline in body weight, kg	0.0 ± 0.6	−1.7 ± 0.6	−0.9 ± 0.6
Difference vs placebo (95% CI)	—	−1.7 ± 0.8 (−3.3, −0.1)	−0.9 ± 0.8 (−2.5, 0.8)
p value		0.035	0.293
Body weight at week 78, kg	91.2 ± 1.9	89.4 ± 1.5	92.7 ± 1.7
Change from baseline in body weight, kg	0.7 ± 0.5	−2.2 ± 0.5	−2.0 ± 0.5
Difference vs placebo (95% CI)	—	−2.9 ± 0.7 (−4.3, −1.5)	−2.8 ± 0.7 (−4.2, −1.3)
p value		<0.001	<0.001

Data are mean ± standard error (s.e.) except for change from baseline values in randomized groups, which are adjusted mean ± s.e. FAS-18 completers: FAS patients who did not discontinue the trial before week 18, had a treatment duration of ≥119 days and had an on-treatment HbA1c value available in that visit window (n = 125 for placebo, n = 132 for empagliflozin 10 mg and n = 117 for empagliflozin 25 mg). FAS-78 completers: FAS patients who did not discontinue before week 78, had a treatment duration of ≥532 days and had an on-treatment HbA1c value available at day 532 or later (n = 112 for placebo, n = 127 for empagliflozin 10 mg and n = 110 for empagliflozin 25 mg). FPG, body weight: ANCOVA in FAS (n = 170 for placebo, n = 169 for empagliflozin 10 mg and n = 155 for empagliflozin 25 mg) using LOCF. HbA1c: ANCOVA in FAS-18 completers or FAS-78 completers using LOCF; insulin dose: ANCOVA in FAS-78 completers (LOCF). ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LOCF, last observation carried forward.

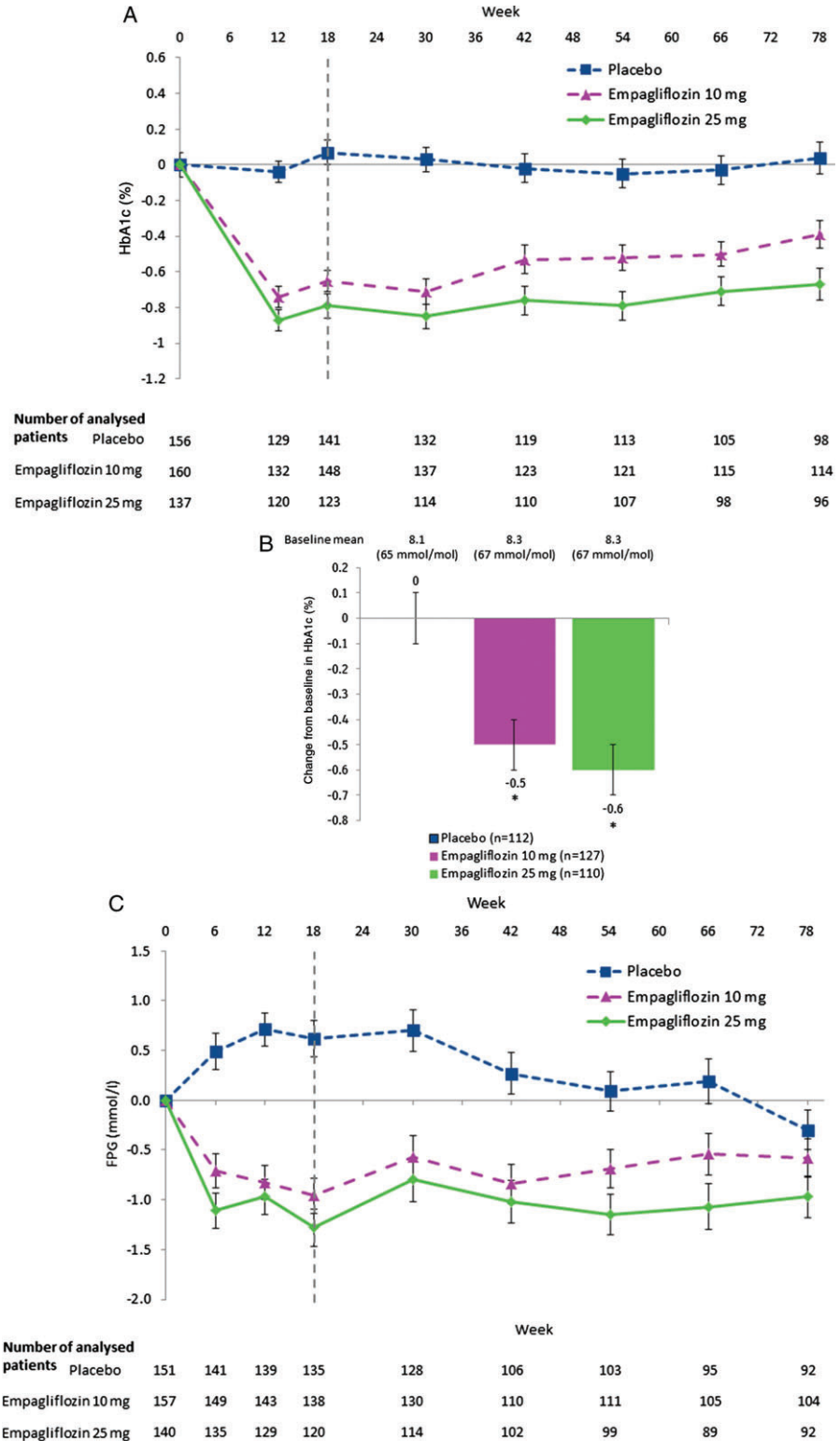
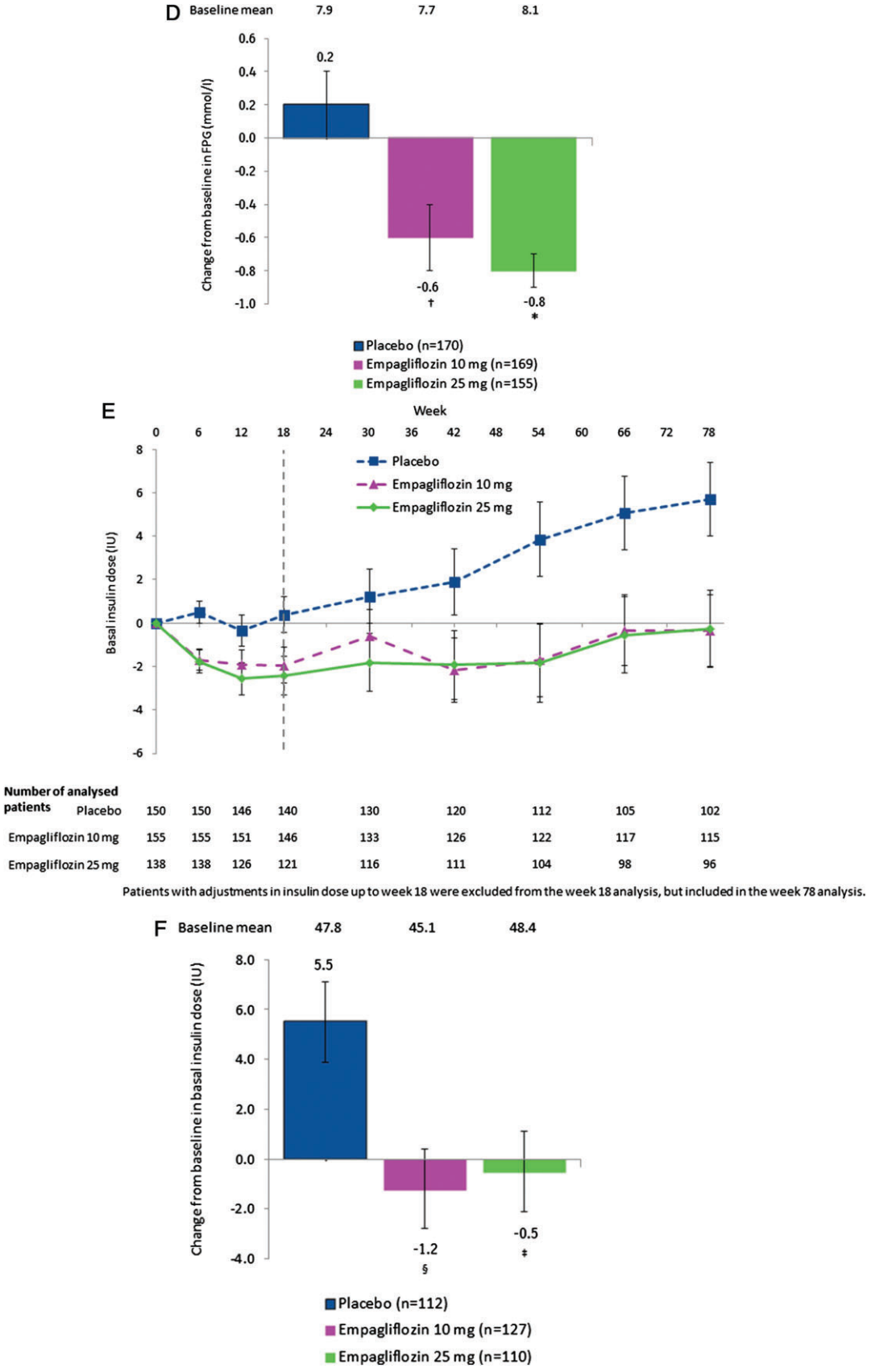


Figure 2. Effect of empagliflozin on efficacy parameters at week 78. (A) Glycated haemoglobin (HbA1c) over time [mixed model repeated measures (MMRM), full analysis set (FAS), observed cases (OC)]; (B) change from baseline in HbA1c [analysis of covariance (ANCOVA), FAS week 78 completers, last observation carried forward (LOCF) imputation]; (C) fasting plasma glucose (FPG) over time (MMRM, FAS, OC); (D) change from baseline in FPG (ANCOVA, FAS, LOCF); (E) basal insulin dose over time (MMRM, FAS, OC); (F) change from baseline in basal insulin dose at week 78 (ANCOVA, FAS-78 completers, LOCF); (G) body weight over time (MMRM, FAS, OC); (H) change from baseline in body weight (ANCOVA, FAS, LOCF); (I) change from baseline in SBP (ANCOVA, FAS, LOCF); (J) change from baseline in DBP (ANCOVA, FAS, LOCF). Data are mean ± standard error (s.e.) at baseline and adjusted mean ± s.e. on treatment. $^{*}p < 0.001$ vs placebo; $^{\dagger}p = 0.005$ vs placebo; $^{\S}p = 0.002$ vs placebo; $^{\ddagger}p = 0.009$ vs placebo; $^{\P}p = 0.004$ vs placebo.



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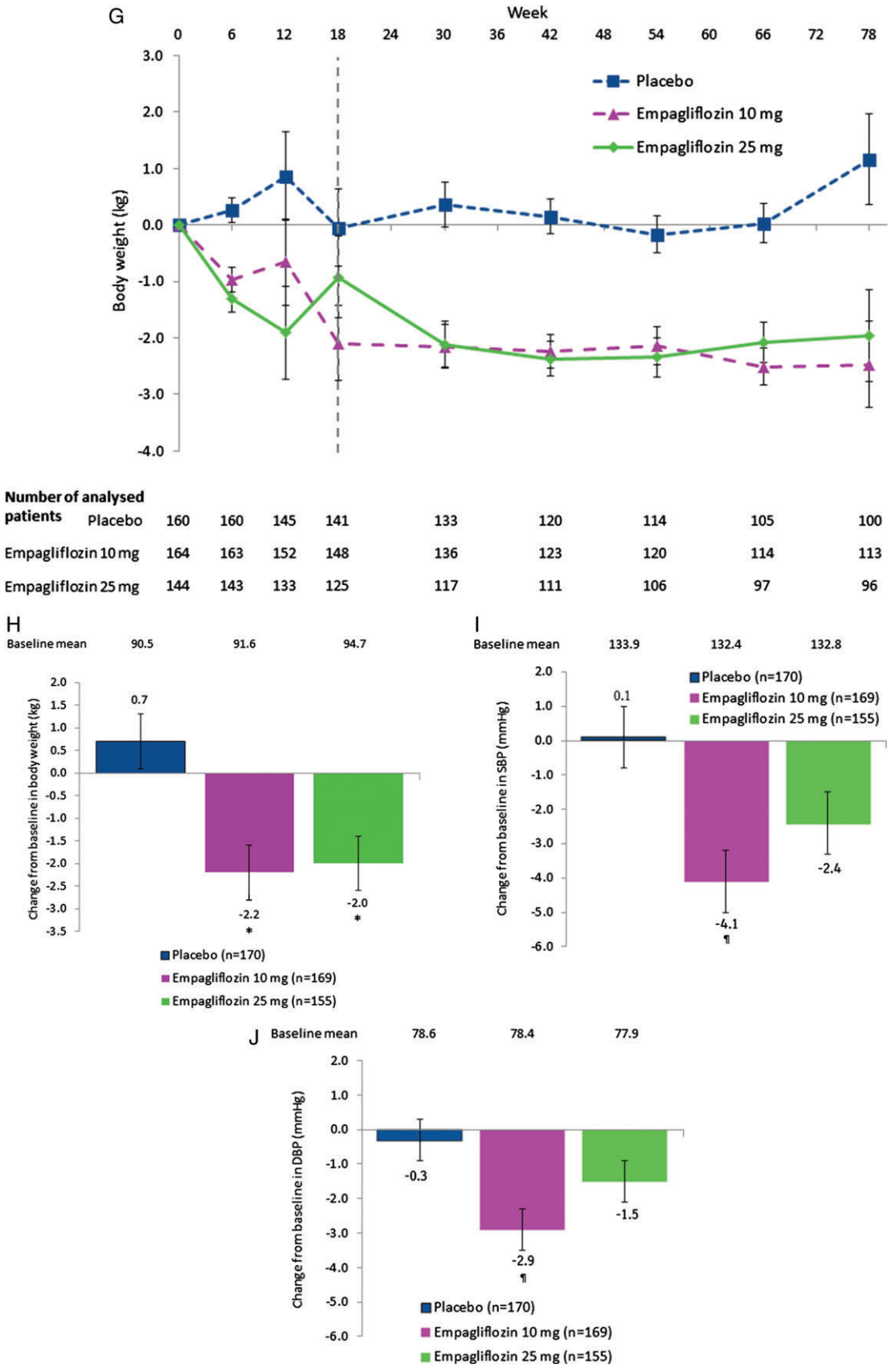

Figure 2. continued

At week 78, mean ± s.e. change from baseline in SBP was greater with empagliflozin 10 mg than with placebo (−4.1 ± 1.0 mmHg vs 0.1 ± 1.0 mmHg; p = 0.004) but the change with empagliflozin 25 mg did not reach significance versus placebo (Figure 2I; Table S3). Adjusted mean ± s.e. changes in DBP were −0.3 ± 0.6 mmHg with placebo compared with −2.9 ± 0.7 mmHg with empagliflozin 10 mg (p = 0.004). The change in DBP with empagliflozin 25 mg did not reach significance versus placebo (Figure 2J; Table S3). No changes in pulse rate were observed.

Safety

Data on AEs are shown in Table 2. The number of patients with ≥1 AE over 78 weeks was similar among the groups. Most events were mild or moderate in intensity.

In the first 18 weeks, confirmed hypoglycaemic AEs were reported in 35 patients (21%) on placebo, 33 patients (20%) on empagliflozin 10 mg and 44 patients (28%) on empagliflozin 25 mg; 1 patient in the empagliflozin 25 mg group required assistance. At week 78, confirmed hypoglycaemic AEs were reported in similar proportions of patients receiving placebo (35%), empagliflozin 10 mg (36%) and empagliflozin 25 mg (36%); 1 additional patient receiving empagliflozin 25 mg required assistance after the fixed insulin dose period.

Over the 78-week treatment period, events consistent with urinary tract infection were reported in fewer patients receiving placebo (9%) than empagliflozin 10 mg (15%) or empagliflozin 25 mg (12%). One patient in each treatment group reported a severe event. Only 1 patient (on empagliflozin 25 mg) experienced an event consistent with urinary tract infection that led to study drug discontinuation and 1 patient (on empagliflozin 25 mg) experienced a urinary tract infection that required hospitalization but did not lead to discontinuation of study drug. Events consistent with urinary tract infection were reported in more female than male patients on placebo (15% vs 3%), empagliflozin 10 mg (26% vs 5%) and empagliflozin 25 mg (18% vs 8%). Most patients who reported an event consistent with urinary tract infection reported only one event (Table 2).

Events consistent with genital infection were reported in a smaller proportion of patients on placebo (2%) than on empagliflozin 10 mg (8%) and empagliflozin 25 mg (5%). All such events were mild or moderate in intensity. Only 1 patient in each empagliflozin group experienced an event consistent with genital infection that led to discontinuation; 1 of these patients (on empagliflozin 10 mg) experienced a genital infection (scrotal abscess) that required hospitalization and surgery, but the event was not considered to be related to study medication. Events consistent with genital infection occurred in more female than male patients on placebo (4% vs 0%) and empagliflozin 25 mg (6% vs 4%) but in similar proportions of female and male patients on empagliflozin 10 mg (8% each). Most patients who reported an event consistent with genital infection reported only one event (Table 2). No diabetic ketoacidosis or ketonuria was reported as an AE.

Changes from baseline in laboratory measurements are shown in Table S4. Small decreases from baseline in uric acid were observed with empagliflozin versus placebo. Electrolyte levels were unchanged across treatment groups. Small increases from baseline in haematocrit were observed with empagliflozin at the end of treatment, which returned to near baseline values at the end of follow-up. There were small decreases from baseline to end of treatment in mean eGFR in every treatment group [mean ± s.d. changes in the follow-up set were −6.3 ± 13.0 (n = 120), −4.8 ± 12.1 (n = 127) and −5.7 ± 13.4 (n = 117) ml/min/1.73 m^2 with placebo, empagliflozin 10 mg and empagliflozin 25 mg, respectively; Table S4]. At follow-up, mean eGFR had fallen further in the placebo group but returned to near baseline levels in the empagliflozin groups (Table S4). No major differences in mean changes from baseline in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were noted between placebo and empagliflozin at week 78 (Table S4).

Discussion

The present study comprised two distinct treatment phases to assess the efficacy and safety of empagliflozin as add-on to basal insulin: an 18-week period during which the insulin dose was to remain fixed, to directly assess the drug effect, followed by a 60-week period in which the insulin dose could be adjusted at the discretion of the investigator with the recommendation to treat to a fasting glucose target. Minimal insulin adjustments were made during this period, as there was no glucose monitoring committee enforcing insulin titrations, probably reflecting clinical practice, in which insulin algorithms are not systematically executed. Treatment with empagliflozin 10 and 25 mg for 18 weeks led to mean reductions from baseline in HbA1c of 0.6 and 0.7% (6.2 and 7.8 mmol/mol), respectively, to mean levels close to 7.5% (58 mmol/mol), in contrast to no change in HbA1c in the placebo group. These reductions in HbA1c were largely sustained up to week 78 despite minimal reductions in the dose of insulin in the empagliflozin groups, contrasting with slight insulin dose increments in the placebo group. The option to adjust basal insulin dose between weeks 18 and 78 differs from previous studies investigating oral agents as add-on to insulin, in which the insulin dose was to remain stable [17–21], and is more akin to clinical practice; however, it is conceivable that greater proportions of patients would have achieved target HbA1c levels had investigators been required to systematically adjust insulin doses.

While an increase in weight was observed with placebo, sustained weight loss was observed in the empagliflozin groups, likely due to urinary glucose excretion and mild osmotic diuresis. Weight control is an important issue in the management of patients with type 2 diabetes, particularly in patients taking insulin [21–23]. It has been estimated that with insulin therapy, a 1% decrease in HbA1c level is associated with a 2-kg weight gain over 1 year [24], and it is remarkable that with empagliflozin, despite a 0.7% reduction in HbA1c, weight was reduced by 2 kg. Weight gain may worsen insulin resistance, resulting in the need for an increased dose of insulin, which may cause further weight gain [23,25], and can reduce patients' adherence to insulin regimens [22]; thus, the decrease in body weight observed with empagliflozin suggests this agent could be of particular benefit when used as add-on to insulin.

Table 2. Summary of adverse events.

	Placebo N = 170	Empagliflozin 10 mg N = 169	Empagliflozin 25 mg N = 155
≥1AE(s)	148 (87)	143 (85)	135 (87)
≥1 drug-related*AE(s)	52 (31)	65 (38)	68 (44)
≥1AE(s) leading to discontinuation	13 (8)	19 (11)	20 (13)
≥1 serious AE(s)	28 (16)	28 (17)	28 (18)
Deaths	1 (1)	0	0
AEs with frequency ≥5% in any group (by preferred term)			
Hypoglycaemia	56 (33)	56 (33)	55 (35)
Nasopharyngitis	22 (13)	20 (12)	17 (11)
Urinary tract infection	13 (8)	21 (12)	16 (10)
Hyperglycaemia	17 (10)	16 (9)	15 (10)
Upper respiratory tract infection	10 (6)	18 (11)	13 (8)
Back pain	13 (8)	11 (7)	13 (8)
Dizziness	12 (7)	18 (11)	7 (5)
Diarrhoea	13 (8)	10 (6)	11 (7)
Nausea	12 (7)	9 (5)	8 (5)
Arthralgia	10 (6)	6 (4)	8 (5)
Cough	9 (5)	6 (4)	4 (3)
Headache	5 (3)	5 (3)	8 (5)
Depression	4 (2)	11 (7)	2 (1)
Vomiting	5 (3)	4 (2)	8 (5)
Fatigue	2 (1)	10 (6)	4 (3)
Hypertension	12 (7)	1 (1)	3 (2)
Confirmed hypoglycaemic AEs [plasma glucose ≤3.9 mmol/l (≤70 mg/dl) and/or requiring assistance]	60 (35)	61 (36)	56 (36)
Symptomatic [glucose concentration ≥3.0 to ≤3.9 mmol/l (≥54 to ≤70 mg/dl) accompanied by typical symptoms of hypoglycaemia but not requiring assistance]†	22 (13)	28 (17)	21 (14)
Symptomatic hypoglycaemic AEs†[glucose concentration <3.0 mmol/l (<54 mg/dl) accompanied by typical symptoms of hypoglycaemia but not requiring assistance]	29 (17)	22 (13)	31 (20)
Severe hypoglycaemic events†(events requiring assistance)	0	0	2 (1)
Events consistent with urinary tract infection‡	15 (9)	25 (15)	18 (12)
By gender			
Male	3 (3)	5 (5)	7 (8)
Female	12 (15)	20 (26)	11 (18)
Number of events per patient			
0	155 (91)	144 (85)	137 (88)
1	10 (6)	20 (12)	12 (8)
2	4 (2)	2 (1)	3 (2)
3 or 4	0	3 (2)	1 (1)
≥5	1 (1)	0	2 (1)
Events consistent with genital infection§	3 (2)	13 (8)	8 (5)
By gender			
Male	0	7 (8)	4 (4)
Female	3 (4)	6 (8)	4 (6)
Number of events per patient			
0	167 (98)	156 (92)	147 (95)
1	3 (2)	11 (7)	7 (5)
2	0	1 (1)	0
3 or 4	0	1 (1)	0
≥5	0	0	1 (1)

Data are number of patients with event (%). Data from treated set. AE, adverse event.
*As reported by the investigator.
†Worst event.
‡Reports of urinary tract infection were based on 70 preferred terms.
§Reports of genital infection were based on 89 preferred terms.

In the present study, empagliflozin led to reductions in SBP compared with placebo, without increases in pulse rate; this may be attributable to a mild osmotic diuretic effect of urinary glucose excretion in combination with weight loss [26]. The improvements in glycaemic control, body weight and blood pressure that have been observed in this and other clinical trials of SGLT2 inhibitors suggest these agents have the potential to reduce cardiovascular risk in patients with type 2 diabetes [27]. An ongoing cardiovascular outcome trial (EMPA-REG OUTCOME™; NCT01131676) is investigating the effect of empagliflozin in patients with type 2 diabetes and high cardiovascular risk.

Empagliflozin was well tolerated when used as add-on to basal insulin. During the first 18 weeks (fixed insulin dose period), the percentage of patients with confirmed hypoglycaemic AEs was slightly higher with empagliflozin 25 mg than with placebo or empagliflozin 10 mg; however, after physicians were allowed to titrate insulin, the percentage of patients with confirmed hypoglycaemic events over the complete 78-week treatment period was similar among the treatment groups, despite a significant decrease in HbA1c in patients treated with empagliflozin compared with placebo. This is important, as hypoglycaemia is a major barrier to achieving glycaemic control in type 2 diabetes, particularly in patients taking insulin [10,28,29]. Further, hypoglycaemia is associated with reduced quality of life and increased macrovascular events and mortality [28,30], while fear of hypoglycaemia may reduce treatment satisfaction and adherence to insulin therapy [10,30,31].

Patients with type 2 diabetes are at increased risk of urinary tract and genital infections [32,33]. In this trial, the proportion of patients with events consistent with urinary tract infection was higher with empagliflozin than placebo, but such events led to study discontinuation in only 1 patient. A greater proportion of patients on empagliflozin than placebo reported events consistent with genital infection, but only 1 patient in each empagliflozin group discontinued the study prematurely because of such an event. Increases in urinary tract and genital infections have been reported in clinical studies with other SGLT2 inhibitors, although cases are generally mild and respond to standard therapy [34,35].

We observed small decreases in eGFR in patients treated with empagliflozin, similar to placebo, which returned to near baseline values at follow-up. Likewise, in a dedicated phase III trial that investigated empagliflozin for 52 weeks (with a 3-week follow-up) in patients with type 2 diabetes and mild, moderate or severe renal impairment found that the small changes in eGFR observed with empagliflozin were reversed within 3 weeks of drug discontinuation [36]. Reversibility of eGFR within the post-treatment follow-up period suggests that these findings may be attributable to renal haemodynamic changes. It has been reported that empagliflozin reduces renal hyperfiltration in patients with type 1 diabetes as a result of preglomerular vasoconstriction [37]. In summary, while a physiological decline in GFR of 2–3 ml/min/1.73 m^2 per year is expected in patients with diabetes [38], renal function appeared to be preserved in both empagliflozin groups at follow-up in the present trial.

The design of the present study was different from those of reported studies of other SGLT2 inhibitors, which were conducted in patients on different insulin regimens at unchanged doses. The present study was conducted in a more homogeneous patient population, as only basal insulin was allowed, and included a flexible insulin dose period that reflects clinical practice [20,21]. In a separate randomized, controlled study, empagliflozin as add-on to multiple daily injections of insulin was shown to improve glycaemic control and reduce weight without increasing hypoglycaemia risk [39].

It is worth noting some limitations of the present study. There was no forced titration of insulin and it appears that the insulin doses were not optimized. The lack of a strict treat-to-target design meant that the full impact of empagliflozin on glucose control and insulin dose could not be established. The study did not control for changes in the use of antihypertensive drugs, which were the most frequent concomitant therapies and this may have influenced the effects observed on blood pressure. Only three-quarters of patients completed the 78-week treatment duration, but sensitivity analyses of the primary analysis to assess the impact of premature discontinuations and important protocol violations were consistent with analyses of primary and key secondary endpoints (Figure 2A; MMRM over time, other sensitivity analyses not shown).

In conclusion, in basal insulin-treated patients with type 2 diabetes with inadequate glycaemic control, empagliflozin 10 and 25 mg once daily for 78 weeks provided improvements in glycaemic control, with a similar risk of hypoglycaemia to placebo, and with reductions in body weight and blood pressure. Empagliflozin was well tolerated except for an increase in genitourinary side effects.

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Conflict of Interest

J. R. has served on scientific advisory boards and received honoraria or consulting fees from companies involved in development of SGLT2 inhibitors including Bristol-Myers Squibb, Roche, Johnson & Johnson, Boehringer Ingelheim and Lexicon. He has also received grants/research support from Pfizer, Roche, Bristol-Myers Squibb, AstraZeneca, Johnson & Johnson, Boehringer Ingelheim and Lexicon. J. R. 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. A. J., C. Z., G. K., U. C. B. and H. J. W. are employees of Boehringer Ingelheim.

J. R. contributed to the study design, acquisition and interpretation of data and reviewed/edited the manuscript. U. C. B.

and H. J. W. contributed to the study design and interpretation of data and reviewed/edited the manuscript. A. J., C. Z. and G. K. contributed to the interpretation of data and reviewed/edited the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Supplementary research design and methods.

Figure S1. Study flow.

Table S1. Patient demographics and baseline characteristics.

Table S2. Percentage of patients with glycated haemoglobin (HbA1c) ≥7.0% (≥53 mmol/mol) at baseline who reached HbA1c <7.0% (<53 mmol/mol) at weeks 18 and 78.

Table S3. Summary of changes in blood pressure at weeks 18 and 78.

Table S4. Laboratory measurements.

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