Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials

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OBJECTIVE

To evaluate the safety and efficacy of empagliflozin 10- and 25-mg doses plus a unique lower dose (2.5 mg) as adjunct to intensified insulin in patients with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

The EASE (Empagliflozin as Adjunctive to inSulin thErapy) program (*N* = 1,707) included two double-blind, placebo-controlled phase 3 trials: EASE-2 with empagliflozin 10 mg (*n* = 243), 25 mg (*n* = 244), and placebo (*n* = 243), 52-week treatment; and EASE-3 with empagliflozin 2.5 mg (*n* = 241), 10 mg (*n* = 248), 25 mg (*n* = 245), and placebo (*n* = 241), 26-week treatment. Together they evaluated empagliflozin 10 mg and 25 mg, doses currently approved in treatment of type 2 diabetes, and additionally 2.5 mg on 26-week change in glycated hemoglobin (primary end point) and weight, glucose time-in-range (>70 to ≤180 mg/dL), insulin dose, blood pressure, and hypoglycemia.

RESULTS

The observed largest mean placebo-subtracted glycated hemoglobin reductions were −0.28% (95% CI −0.42, −0.15) for 2.5 mg, −0.54% (−0.65, −0.42) for 10 mg, and −0.53% (−0.65, −0.42) for 25 mg (all *P* < 0.0001). Empagliflozin 2.5/10/25 mg doses, respectively, reduced mean weight by −1.8/−3.0/−3.4 kg (all *P* < 0.0001); increased glucose time-in-range by +1.0/+2.9/+3.1 h/day (*P* < 0.0001 for 10 and 25 mg); lowered total daily insulin dose by −6.4/−13.3/−12.7% (all *P* < 0.0001); and decreased systolic blood pressure by −2.1/−3.9/−3.7 mmHg (all *P* < 0.05). Genital infections occurred more frequently on empagliflozin. Adjudicated diabetic ketoacidosis occurred more with empagliflozin 10 mg (4.3%) and 25 mg (3.3%) but was comparable between empagliflozin 2.5 mg (0.8%) and placebo (1.2%). Severe hypoglycemia was rare and frequency was similar between empagliflozin and placebo.

CONCLUSIONS

Empagliflozin improved glycemic control and weight in T1D without increasing hypoglycemia. Ketoacidosis rate was comparable between empagliflozin 2.5 mg and placebo but increased with 10 mg and 25 mg. Ketone monitoring for early ketoacidosis detection and intervention and lower empagliflozin doses may help to reduce this risk.

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Type 1 diabetes (T1D), an autoimmune disease characterized by insulin deficiency, affects 30 million people worldwide and is associated with reduced life expectancy owing to acute and chronic complications (1–4). The Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Control and Complications (EDIC) study have shown that improved glucose control by insulin intensification in T1D reduces the long-term risks of microvascular and macrovascular events (4).

Attaining and sustaining glycated hemoglobin (HbA_{1c}) targets via insulin optimization strategies remains a major challenge owing to treatment complexity, increased hypoglycemia, and potential for weight gain. Despite advances in insulin formulations, delivery systems, and glucose monitoring, only one-third of patients are able to achieve glycemic targets and many become overweight or obese (3,5,6). Consequently, there is a need to evaluate available safe and effective treatment options to overcome suboptimal glucometabolic control in T1D. In this regard, the evaluation of some therapies, proven to be effective in type 2 diabetes (T2D), as adjunct to insulin represents a promising strategy (7–9).

Based on their insulin-independent glucosuric mechanism, sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been shown in T1D clinical trials to improve glucometabolic outcomes (10–13). However, an increased risk of diabetic ketoacidosis (DKA) has raised valid clinical concern (14). Interestingly, previous trials in patients with T1D have tested the same doses of SGLT2i used in T2D patients despite potential differences in renal response (15).

Empagliflozin, a highly selective SGLT2i, is approved for use in adults with T2D to improve glycemic control and to reduce the risk of cardiovascular death (16). Phase 2 trials with empagliflozin have shown promise in T1D (17–24). We present the totality of the empagliflozin phase 3 data as adjunctive to insulin in T1D including the characterization of a unique lower dose.

RESEARCH DESIGN AND METHODS

Clinical Trial Design and Conduct

The EASE (Empagliflozin as Adjunctive to inSulin thErapy) program in patients with T1D included two international, multicenter, phase 3, randomized, double-blind, placebo-controlled, parallel-group trials of once-daily oral empagliflozin doses conducted over 52 weeks (EASE-2) and 26 weeks (EASE-3). The treatment period was preceded by a 6-week insulin intensification period and a 2-week placebo run-in period and followed by a 3-week safety follow-up. Empagliflozin 10 mg and 25 mg versus placebo were studied in both trials, and an additional arm (empagliflozin 2.5 mg) was included in EASE-3 in order to characterize a lower effective and safe dose (Supplementary Figure 1). The design and conduct of EASE-2 and EASE-3 were identical with the exception of the following differences in EASE-3: a shorter treatment duration, the assessment of continuous glucose monitoring (CGM) as a substudy, and the inclusion of a lower dose (2.5 mg).

In EASE-2/EASE-3, respectively, 1,338/1,751 patients were screened by 131/189 centers across 17/24 countries; 1,015/1,353 started the placebo run-in period, of which 730/977 were randomized with stratification for type of insulin therapy, estimated glomerular filtration rate (eGFR), HbA_{1c}, and, in EASE-3, also by participation in the CGM substudy.

Trial protocols and informed consent forms were approved by institutional review boards. Patients provided consent prior to enrollment. Adjudication of cardiovascular events, severe hypoglycemia, DKA, and hepatic events was performed by masked, independent clinical event committees. Trial progress and safety were assessed by an unmasked and independent data monitoring committee. Trials were sponsored by Boehringer Ingelheim. See Supplementary Data for details.

Trial Patients

Key inclusion criteria included the following: adult patients with eGFR $\geq$30 mL/min/1.73 m^2, BMI $\geq$18.5 kg/m^2, fasting C-peptide value $<$0.7 ng/mL ($<$0.23 nmol/L), T1D diagnosis $\geq$1 year, insulin needs of 0.3–1.5 units/kg on multiple daily injections or continuous subcutaneous insulin infusion, and HbA_{1c} 7.5–10.0% following the lead-in insulin intensification period. The HbA_{1c} range of 7.5–10.0% at randomization enabled the inclusion of a broad population of patients with T1D at less than optimal glycemic targets despite insulin intensification. This range was also selected in light of the HbA_{1c} superiority trial design followed in EASE-2 and EASE-3. Key exclusion criteria included use of noninsulin antihyperglycemic drugs or severe hypoglycemia or DKA within 3 months of inclusion. See Supplementary Data for the detailed list of inclusion/exclusion criteria.

Trial Procedures

Patients underwent a 6-week investigator-guided insulin intensification period that resulted in changes to HbA_{1c} in addition to body weight and total daily insulin dose from the screening visit to baseline. The EASE-2/EASE-3 mean changes $\pm$ SD in HbA_{1c}, body weight, and total daily insulin dose during this pretreatment period were, respectively, $-0.6 \pm 0.6\%$/$-0.5 \pm 0.7\%$, $+0.6 \pm 2$ kg/$+0.5 \pm 2$ kg, and $+5 \pm 29\%$/$+3 \pm 16\%$. The insulin regimen was to remain stable during a subsequent 2-week placebo run-in period. Trial medication was taken once daily and adherence was evaluated at clinic visits. If HbA_{1c} was $<$8.0% at randomization, total insulin dose was reduced by 10% to lower hypoglycemia risk. During the insulin intensification pretreatment phase and throughout the entire duration of randomized treatment, investigators were unblinded to glycemic markers (e.g., fasting plasma glucose, HbA_{1c}, etc.), and could freely adjust the insulin regimen according to their clinical discretion and based on local guidelines to achieve the best standard of care. In addition, guidance to avoid substantial insulin dose reduction was provided. During the entire trial period, including the prerandomization period, insulin dose levels (total, basal, bolus) were determined based on patient-reported information collected on a daily basis in an electronic diary; data were averaged over a 2-week period before the time point of assessment.

All patients received a point-of-care device capable of measuring blood glucose and β-hydroxybutyrate (BHB). Patients were educated on ketone monitoring when feeling unwell (e.g., illness, symptoms suggestive of DKA irrespective of the glucose value) and to seek medical care in case of increased BHB ($>$1.5 mmol/L). The BHB threshold of $>$1.5 mmol/L was chosen based on recommendations provided in the user manual of the ketone meter and in light

of the fact that patients are at a higher risk of developing DKA above this BHB level (25). During run-in and the first 4 weeks of treatment, fasting BHB was tested daily to provide initial background information irrespective of symptoms, and 2–3 times/week subsequently. All patients were also provided with an electronic diary for daily recording of glucose self-monitoring results, hypoglycemic events, insulin intake, and BHB measurements. A masked CGM system (Dexcom G4, blinded mode) was used in EASE-2 in all patients (and as a substudy in EASE-3) to assess glycemic profile at baseline (over 2 weeks) and on treatment (over 4 weeks and 2 weeks in EASE-2 and EASE-3, respectively). See Supplementary Data for detailed trial procedures.

End Points

The primary end point in both studies was the change from baseline in HbA_{1c} at week 26. Key secondary end points were investigator-reported symptomatic hypoglycemia with confirmed blood glucose <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemia requiring third-party assistance from weeks 5 to 26 as well as from weeks 1 to 26. The week 5 to 26 time window was chosen as the first step for the key secondary hypoglycemia analysis in order to generate data on a stable insulin background by excluding the initial phase of therapy (weeks 1 to 4), when insulin dose adjustments are more likely to occur. In EASE-2, change from baseline in body weight at week 26, percentage of time spent in target glucose range of >70 to ≤180 mg/dL (>3.9 to ≤10.0 mmol/L) and interquartile range (IQR) as determined by CGM in weeks 23 to 26, total daily insulin dose at week 26, and systolic/diastolic blood pressure at week 26 were also evaluated as key secondary end points. These parameters were also evaluated in EASE-3; CGM-based assessments were, however, done in a substudy. Safety evaluations consisted of adverse event (AE) reporting, laboratory tests, and vital signs. Definitions of hypoglycemia, DKA categories, and the AEs of interest are outlined in Supplementary Data.

Statistical Analyses

A two-sided *t* test (type I error $\alpha = 2.5\%$) provides 90% power to detect an HbA_{1c} change of −0.3% between empagliflozin (10 and 25 mg) and placebo using 225 evaluable patients per arm (SD = 0.9%). To allow for attrition, 240 patients per arm were planned.

The primary end point was analyzed using a mixed-effects model for repeated measures (MMRM) with Bonferroni-adjusted comparisons between empagliflozin 10 or 25 mg and placebo (each dose tested at the two-sided level of $\alpha = 2.5\%$). The primary efficacy analysis included on-treatment data only as observed cases (OC) on the full analysis set (FAS), including all treated patients with a baseline and ≥1 on-treatment HbA_{1c} measurements. Subsequently, an effectiveness analysis including data after treatment discontinuation (OC-AD) was performed hierarchically on the modified intention-to-treat set (mITT), including all treated patients with a baseline and ≥1 postrandomization HbA_{1c} measurements. If efficacy and effectiveness null hypotheses were rejected, then sequentially the primary efficacy end point for empagliflozin 2.5 mg in EASE-3 (on-treatment data) and key secondary end points in both trials were to be tested for empagliflozin 10 and 25 mg versus placebo in a confirmatory way. A negative binomial model was used to analyze investigator-reported hypoglycemia. An MMRM model was used to analyze changes in weight, insulin dose, and blood pressure. In EASE-2, ANCOVA was used for CGM analyses. All analyses were prespecified except for patient-reported nocturnal hypoglycemia (Fig. 2*B*), net benefit analysis (Supplementary Fig. 14), and DKA subgroup analyses (Supplementary Table 2). See Supplementary Data for details on statistical methods.

RESULTS

Patient Characteristics

Overall, 1,338 patients were screened and 730 were assigned treatment in EASE-2, while 1,751 were screened and 977 were assigned treatment in EASE-3 (Supplementary Fig. 2). More than 90% of patients completed week 26 and were included in the full analysis (Supplementary Fig. 2). The study population was half female with average baseline age of low to mid-40s, largely white, and recruited primarily in Europe and North America. Patients had normal blood pressure and kidney function at baseline with <4% of the overall population having an eGFR <60 mL/min/1.73 m^2. Average baseline HbA_{1c} was 8.1–8.2% with insulin needs of approximately 0.7 units/kg (with equal basal-bolus split). Insulin pumps were used in approximately one-third of patients. Baseline characteristics were balanced (Table 1).

Primary Efficacy End Point

Empagliflozin improved glycemic control, as assessed by placebo-corrected HbA_{1c} change after 26 weeks of treatment (Fig. 1). All empagliflozin doses led to statistically significant HbA_{1c} reductions with consistency across the trials and between the primary efficacy and effectiveness analyses (Fig. 1*B* and Supplementary Fig. 3). Maximal HbA_{1c} effect was observed from week 12 and largely sustained up to the end of the trials (Fig. 1*A* and *B*). Mean HbA_{1c} reduction after 26 weeks of treatment was dose-dependent and greatest with empagliflozin 10- and 25-mg doses (up to −0.54%; $P < 0.0001$). Empagliflozin 2.5 mg also reduced HbA_{1c} (−0.28%; $P < 0.0001$). The largest placebo-corrected HbA_{1c} reduction occurred in patients with baseline HbA_{1c} ≥8%, consisting of ∼60% of the study population (2.5 mg, −0.35%; 10 mg, up to −0.70%; 25 mg, up to −0.64%; $P < 0.0001$), as shown in Fig. 1*C*.

Key Secondary Efficacy End Points

After 26 weeks of treatment, empagliflozin resulted in placebo-corrected reduction in body weight (up to −3.4 kg; $P < 0.0001$), systolic blood pressure (up to −3.9 mmHg; $P < 0.0001$), and diastolic blood pressure (up to −2.3 mmHg; $P = 0.0006$) with overall comparable results for 10 and 25 mg across studies (Table 2 and Supplementary Figs. 4–6). In EASE-2, empagliflozin doses 10 and 25 mg significantly increased CGM-derived glucose time in range (up to 3.1 h/day; $P < 0.0001$) and decreased glycemic variability assessed by IQR (up to −19 mg/dL; $P < 0.0001$) (Table 2 and Supplementary Fig. 7). In EASE-3, empagliflozin 2.5 mg followed the same beneficial trend as the 10- and 25-mg doses with respect to improvements in weight (−1.8 kg; $P < 0.0001$), systolic blood pressure (−2.1 mmHg; $P = 0.027$), glucose time in range (+1 h/day; $P = 0.1063$), and IQR (−7.9 mg/dL; $P = 0.1096$). Total insulin dose was also significantly decreased on empagliflozin versus

Table 1—Baseline characteristics

Characteristics	EASE-2			EASE-3			
	Empagliflozin 10 mg (*N* = 243)	Empagliflozin 25 mg (*N* = 241)	Placebo (*N* = 239)	Empagliflozin 2.5 mg (*N* = 237)	Empagliflozin 10 mg (*N* = 244)	Empagliflozin 25 mg (*N* = 242)	Placebo (*N* = 238)
Female	125 (51.4)	130 (53.9)	130 (54.4)	119 (50.2)	130 (53.3)	119 (49.2)	124 (52.1)
Age, years	45.7 ± 12.5	45.3 ± 13.9	44.5 ± 13.5	43.4 ± 14.2	42.4 ± 13.3	44.2 ± 13.5	42.2 ± 13.2
Race							
White	230 (94.7)	227 (94.2)	225 (94.1)	233 (98.3)	232 (95.1)	228 (94.2)	223 (93.7)
Black/African American	6 (2.5)	4 (1.7)	8 (3.3)	4 (1.7)	10 (4.1)	4 (1.7)	5 (2.1)
Asian	6 (2.5)	10 (4.1)	8 (3.3)	3 (1.3)	2 (0.8)	5 (2.1)	2 (0.8)
Other	1 (0.4)	0	0	0	1 (0.4)	5 (2.1)	8 (3.4)
Region							
Europe	131 (53.9)	130 (53.9)	133 (55.6)	156 (65.8)	148 (60.7)	150 (62.0)	148 (62.2)
North America	95 (39.1)	94 (39.0)	91 (38.1)	60 (25.3)	61 (25.0)	60 (24.8)	63 (26.5)
Pacific	12 (4.9)	10 (4.1)	10 (4.2)	7 (3.0)	12 (4.9)	11 (4.5)	5 (2.1)
Latin America	0	0	0	12 (5.1)	10 (4.1)	14 (5.8)	19 (8.0)
Africa	0	0	0	2 (0.8)	13 (5.3)	7 (2.9)	3 (1.3)
Asia	5 (2.1)	7 (2.9)	5 (2.1)	0	0	0	0
Diabetes duration, years	22.8 ± 12.6	22.5 ± 13.0	22.4 ± 12.4	20.8 ± 11.9	20.5 ± 11.9	21.2 ± 11.4	21.7 ± 13.0
HbA_{1c}, %	8.10 ± 0.60	8.06 ± 0.53	8.13 ± 0.57	8.14 ± 0.61	8.19 ± 0.64	8.19 ± 0.65	8.19 ± 0.58
<8.0%	105 (43.2)	109 (45.2)	108 (45.2)	101 (42.6)	106 (43.4)	98 (40.5)	98 (41.2)
≥8.0%	138 (56.8)	132 (54.8)	131 (54.8)	136 (57.4)	138 (56.6)	144 (59.5)	140 (58.8)
Weight, kg	86.2 ± 18.2	85.6 ± 18.3	83.4 ± 16.7	81.6 ± 14.6	83.7 ± 17.0	83.3 ± 18.9	80.7 ± 16.9
BMI, kg/m^2*	29.5 ± 5.5	29.5 ± 6.0	28.5 ± 5.3	28.0 ± 4.4	28.7 ± 5.1	28.4 ± 5.6	27.8 ± 5.1
eGFR, $mL/min/1.73\ m^2$	95.0 ± 18.1	94.1 ± 18.9	95.9 ± 18.4	96.5 ± 19.9	97.3 ± 19.9	95.7 ± 19.7	97.8 ± 19.3
≥60	236 (97.1)	232 (96.3)	232 (97.1)	227 (95.8)	234 (95.9)	228 (94.2)	230 (96.6)
<60	7 (2.9)	9 (3.7)	7 (2.9)	10 (4.2)	10 (4.1)	14 (5.8)	8 (3.4)
Blood pressure, mmHg							
Systolic	124.0 ± 15.5	125.0 ± 14.9	124.7 ± 15.7	123.5 ± 14.6	125.1 ± 15.1	124.6 ± 15.0	120.6 ± 14.8
Diastolic	75.8 ± 9.3	77.2 ± 9.2	75.6 ± 9.9	75.2 ± 8.9	76.9 ± 8.7	75.4 ± 9.2	74.7 ± 9.1
Total daily insulin dose, units/kg†	0.70 ± 0.24	0.74 ± 0.26	0.70 ± 0.23	0.70 ± 0.24	0.71 ± 0.24	0.71 ± 0.24	0.70 ± 0.24
Basal insulin dose‡	0.36 ± 0.16	0.38 ± 0.17	0.37 ± 0.14	0.36 ± 0.14	0.37 ± 0.14	0.37 ± 0.15	0.36 ± 0.15
Bolus insulin dose¶	0.34 ± 0.15	0.36 ± 0.17	0.35 ± 0.17	0.36 ± 0.17	0.35 ± 0.15	0.35 ± 0.15	0.35 ± 0.16
Type of insulin							
MDI	144 (59.3)	143 (59.3)	142 (59.4)	156 (65.8)	162 (66.4)	161 (66.5)	157 (66.0)
CSII	99 (40.7)	98 (40.7)	97 (40.6)	81 (34.2)	82 (33.6)	81 (33.5)	81 (34.0)

Data are *n* (%) or means ± SD. The eGFR at baseline was estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation. CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections. *EASE-3: *n* = 236 for empagliflozin 2.5 mg. †EASE-2: *n* = 230 for empagliflozin 10 mg, *n* = 226 for empagliflozin 25 mg, *n* = 226 for placebo; EASE-3: *n* = 224 for empagliflozin 2.5 mg, *n* = 221 for empagliflozin 10 mg, *n* = 226 for empagliflozin 25 mg, *n* = 223 for placebo. ‡EASE-2: *n* = 184 for empagliflozin 10 mg, *n* = 186 for empagliflozin 25 mg, *n* = 172 for placebo; EASE-3: *n* = 192 for empagliflozin 2.5 mg, *n* = 190 for empagliflozin 10 mg, *n* = 189 for empagliflozin 25 mg, *n* = 187 for placebo. ¶EASE-2: *n* = 186 for empagliflozin 10 mg, *n* = 187 for empagliflozin 25 mg, *n* = 170 for placebo; EASE-3: *n* = 189 for empagliflozin 2.5 mg, *n* = 190 for empagliflozin 10 mg, *n* = 187 for empagliflozin 25 mg, *n* = 187 for placebo.

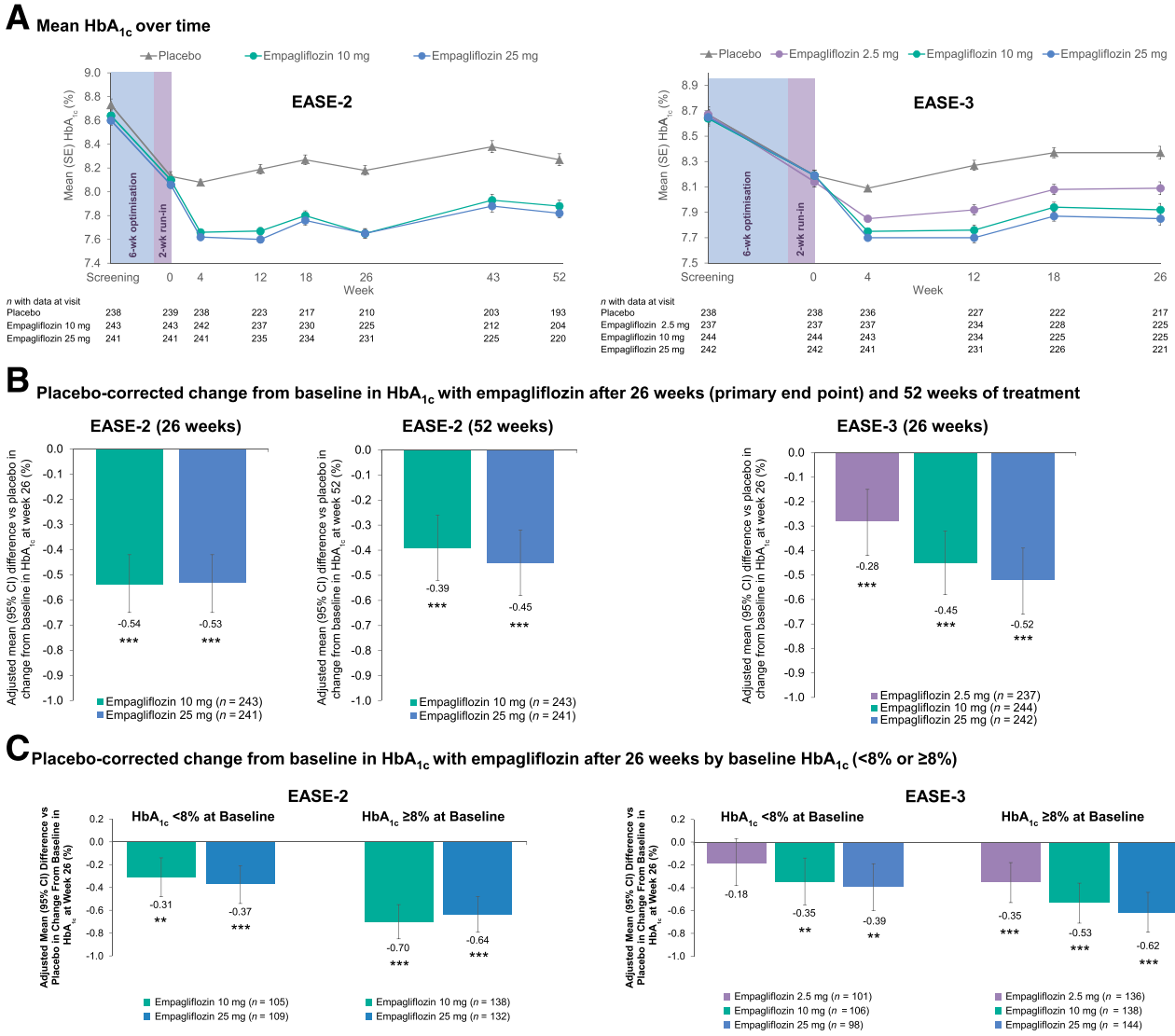


Figure 1—HbA_{1c} efficacy analysis: Data are from patients treated with ≥1 dose of study drug who had a baseline and ≥1 on-treatment HbA_{1c} measurement. *A*: HbA_{1c} from screening to week 52 (EASE-2) and week 26 (EASE-3). Values at screening and week 0 are descriptive data. Values at weeks 4–52 are based on mixed-model repeated measures analysis. *B*: Placebo-corrected change from baseline in HbA_{1c} with empagliflozin at week 26 (primary end point in EASE-2 and EASE-3) and week 52 (EASE-2). Data are based on mixed-model repeated measures analysis. ***$P < 0.0001$ for difference vs. placebo. *C*: Placebo-corrected change from baseline in HbA_{1c} with empagliflozin at week 26 in subgroups by baseline HbA_{1c} (<8% and ≥8%). Data are based on mixed-model repeated measures analysis. **$P < 0.001$ for difference vs. placebo; ***$P < 0.0001$ for difference vs. placebo.

placebo after 26 weeks of treatment: up to −13.3% and −12.7% for empagliflozin 10- and 25-mg doses, respectively, and −6.4% for the 2.5-mg dose (Table 2 and Supplementary Fig. 8). The need to reduce insulin dose when initiating empagliflozin occurred shortly after the start of therapy, and the total daily insulin dose was largely stabilized by week 4 of treatment as assessed by patient-reported insulin dose levels (Supplementary Fig. 8). Importantly, the total daily insulin dose in patients assigned to placebo was relatively stable over the entire treatment period and comparable to the level reported following the end of the prerandomization insulin intensification period. For patients assigned to empagliflozin, the placebo-corrected insulin dose reduction was equivalent between basal/bolus components after 26 weeks of treatment: −0.02/−0.03 units/kg for 2.5 mg, up to −0.05/−0.05 units/kg for 10 mg, and up to −0.05/−0.04 units/kg for 25 mg (Supplementary Figs. 9 and 10). Empagliflozin also reduced fasting plasma glucose (up to −35.2 mg/dL; $P < 0.0001$) and waist circumference (up to −2.9 cm; $P < 0.0001$) versus placebo after 26 weeks of treatment (Supplementary Figs. 11 and 12).

Hypoglycemia

Over treatment weeks 5 to 26, empagliflozin 2.5, 10, and 25 mg did not increase the rate of investigator-reported symptomatic hypoglycemia (<54 mg/dL) or severe hypoglycemia (Fig. 2*A*). However, these investigator-reported events (classified by investigators as AEs based on their clinical review and judgment) represented only a subset of the patient-reported symptomatic events (<54 mg/dL) captured by electronic diary (a total of

Table 2—Secondary outcomes

	Empagliflozin 2.5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg	*P* value for differences vs. placebo
Weight, kg				
EASE-2 (26 weeks)	—	−2.7	−3.3	<0.0001 for both doses
EASE-2 (52 weeks)*	—	−3.2	−3.6	<0.0001 for both doses*
EASE-3 (26 weeks)	−1.8*	−3.0	−3.4	<0.0001 for all
CGM-derived time in glucose range of >70 to ≤180 mg/dL, % (h/day)				
EASE-2 (26 weeks)	—	+11.9 (+2.9 h/day)	+12.9 (+3.1 h/day)	<0.0001 for both doses
EASE-2 (52 weeks)*	—	+12.2 (+2.9 h/day)	+12.5 (+3.0 h/day)	<0.0001 for both doses*
EASE-3 (26 weeks)†	+4.3 (+1.0 h/day)	+10.7 (+2.6 h/day)	+7.4 (+1.8 h/day)	<0.0001 for 10 mg; <0.01 for 25 mg
CGM-derived IQR, mg/dL				
EASE-2 (26 weeks)	—	−16.9	−19.0	<0.0001 for both doses
EASE-2 (52 weeks)*	—	−19.8	−19.4	<0.0001 for both doses*
EASE-3 (26 weeks)†	−7.9	−14.6	−10.7	<0.01 for 10 mg; <0.05 for 25 mg
Total daily insulin dose, %				
EASE-2 (26 weeks)	—	−13.3	−12.7	<0.0001 for both doses
EASE-2 (52 weeks)*	—	−12.0	−12.9	<0.0001 for both doses*
EASE-3 (26 weeks)	−6.4	−9.5	−12.6	<0.0001 for all
SBP/DBP, mmHg				
EASE-2 (26 weeks)	—	−2.1/−1.3	−3.7/−2.3	SBP: <0.05 for 10 mg*; <0.001 for 25 mg DBP: <0.05 for 10 mg*; <0.001 for 25 mg
EASE-2 (52 weeks)*	—	−3.4/−1.7	−4.7/−1.5	SBP: <0.01 for 10 mg*; <0.0001 for 25 mg* DBP: <0.05 for both doses*
EASE-3 (26 weeks)	−2.1/−0.3	−3.9/−1.7	−3.7/−1.4	SBP: <0.05 for 2.5 mg*; <0.0001 for 10 mg and 25 mg DBP: <0.01 for 10 mg*; <0.05 for 25 mg*

Data are adjusted mean differences vs. placebo in changes from baseline based on mixed-model repeated measures, except for EASE-2 CGM data at week 26, which were performed using ANCOVA. Analyses were performed in randomized patients treated with ≥1 dose of study drug who had a baseline and ≥1 on-treatment HbA_{1c} measurement. DBP, diastolic blood pressure; SBP, systolic blood pressure. *Nominal. †Substudy.

12,790 investigator-reported events out of a total of 23,147 patient-reported events, representing 55%). For this reason, we present both investigator- and patient-reported events in Fig. 2*A* and *B*, respectively.

During the initial phase of insulin adjustment (weeks 1–4), the rate of investigator-reported severe and symptomatic hypoglycemic AEs (<54 mg/dL) was similar (Supplementary Fig. 13). Based on pooled safety analyses, the rate of adjudicated severe hypoglycemia was also similar between empagliflozin and placebo (Table 3).

Based on the totality of all hypoglycemia events reported by patients, empagliflozin 10 and 25 mg significantly reduced the rate of patient-reported symptomatic hypoglycemia (<54 mg/dL) as recorded in electronic diaries up to treatment week 52 (Fig. 2*B*). Empagliflozin 2.5 mg also showed a similar beneficial 26-week trend in EASE-3. Nocturnal symptomatic hypoglycemia (<54 mg/dL) was also reduced with empagliflozin, including the 2.5-mg dose, up to 37% relative to placebo (Fig. 2*B*).

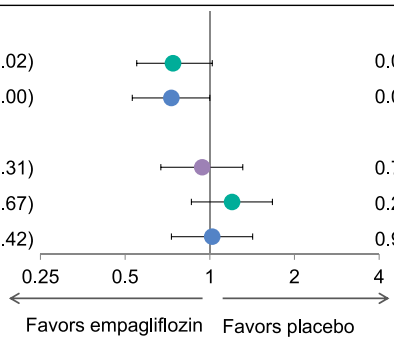
General Safety and DKA

Genital infections and generally volume depletion occurred with higher frequency with empagliflozin than placebo (Table 3). Urinary tract infections, hepatic events, acute renal impairment, and bone fractures occurred with similar frequency on empagliflozin versus placebo. One minor toe amputation was reported on empagliflozin 2.5 mg in a patient with a history of amputations and peripheral arterial disease. DKA data suggested dose-dependent risk. For confirmed adjudicated DKA (case definition "certain"), the rate in patients on empagliflozin 2.5 mg was low and similar to placebo (0.8%, 1.2%; respectively), while the rate was higher in the empagliflozin 10- and 25-mg groups compared with placebo (4.3%, 3.3%, and 1.2%, respectively). There were few severe DKA cases overall with a trend toward more severe cases on empagliflozin 25 mg, including one fatal case mainly related to delayed DKA diagnosis and treatment (refer to Supplementary Data for details).

Patients with DKA generally had at least one precipitating factor, such as a concomitant illness/infection or reduced insulin intake (Supplementary Table 1). Based on baseline subgroup analyses, female sex and insulin pump use were identified as important DKA risk factors in pooled analyses across EASE-2 and EASE-3 for placebo and empagliflozin 10-mg and 25-mg dose groups (Supplementary Table 2). Specifically, of the 72 patients with adjudicated certain or potential DKA, 48 patients were insulin pump users, while 24 were multiple daily injection users; 53 patients were female, while 19 were male. Of the 38 patients who had both risk factors (female sex and insulin pump use) and a confirmed adjudicated DKA event, 2 were in the placebo group (representing 1.8% of female patients on pump in this group), 21 were in the empagliflozin 10-mg group (representing 20.4% of

A **Investigator-reported symptomatic hypoglycemic adverse events with blood glucose <54 mg/dL and/or severe hypoglycemic events**

	Empagliflozin		Placebo		Event Rate Ratio (95% CI)	Event Rate Ratio (95% CI)	*P* value
	N	*no. of events*	*N*	*no. of events*			
EASE-2 (week 5–26)							
Empagliflozin 10 mg	243	1051	238	1535	0.74 (0.55, 1.02)		0.0623
Empagliflozin 25 mg	239	994	238	1535	0.73 (0.53, 1.00)		0.0480
EASE-3 (week 5–26)							
Empagliflozin 2.5 mg	237	749	235	1052	0.94 (0.67, 1.31)		0.7186
Empagliflozin 10 mg	241	1083	235	1052	1.20 (0.86, 1.67)		0.2752
Empagliflozin 25 mg	237	941	235	1052	1.02 (0.73, 1.42)		0.9077



B **Patient-reported symptomatic hypoglycemic events with blood glucose <54 mg/dL**

	Empagliflozin		Placebo		Event Rate Ratio (95% CI)	Event Rate Ratio (95% CI)	*P* Value
	N	*no. of events*	*N*	*no. of events*			
All events							
Empagliflozin 2.5 mg	241	1936	241	2236	0.85 (0.67, 1.08)		0.1876
Empagliflozin 10 mg	491	6281	484	8501	0.77 (0.65, 0.90)		0.0014
Empagliflozin 25 mg	489	6429	484	8501	0.79 (0.67, 0.92)		0.0035
Nocturnal events							
Empagliflozin 2.5 mg	241	292	241	443	0.66 (0.48, 0.91)		0.0114
Empagliflozin 10 mg	491	973	484	1587	0.63 (0.52, 0.78)		<0.0001
Empagliflozin 25 mg	489	1114	484	1587	0.72 (0.59, 0.88)		0.0014

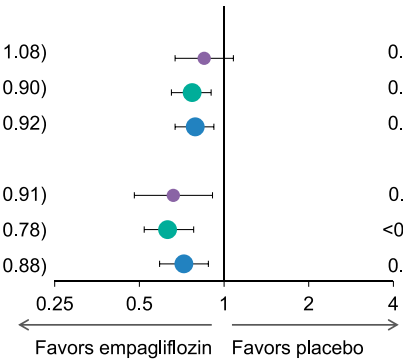


Figure 2—Hypoglycemia. *A*: Investigator-reported symptomatic hypoglycemic adverse events with blood glucose <54 mg/dL and/or severe hypoglycemic events in weeks 5–26 (key secondary hypoglycemia end point); analyses were performed using a negative binomial model in randomized patients treated with ≥1 dose of study drug who had a baseline and ≥1 on-treatment HbA_{1c} measurement. During the initial phase of insulin adjustments (weeks 1–4), event rates between empagliflozin and placebo were similar (Supplementary Fig. 13). *B*: Patient-reported symptomatic hypoglycemic events with blood glucose <54 mg/dL (totality of all reported events by patients). EASE-3 data from baseline to week 26 are presented for empagliflozin 2.5 mg, and pooled EASE-2 and EASE-3 data from baseline to week 52 are presented for empagliflozin 10 mg and empagliflozin 25 mg. Nocturnal episodes were those with onset between 0000 h and 0559 h. Analyses were performed using a negative binomial model in randomized patients treated with ≥1 dose of study drug.

female patients on pump in this dose group), and 15 were in the empagliflozin 25-mg group (representing 15.2% of female patients on pump in this dose group).

Overall Net Benefit

An exploratory post hoc net clinical benefit analysis found that a greater proportion of patients on empagliflozin (+23–38%) relative to placebo-treated patients achieved the end point that included HbA_{1c} reduction of at least −0.3% without weight gain, without occurrences of adjudicated DKA, and without severe hypoglycemia (Supplementary Fig. 14). The observed clinical benefit was consistent across a range of HbA_{1c} thresholds (Supplementary Fig. 14).

CONCLUSIONS

The empagliflozin T1D program was a comprehensive evaluation of the benefit-risk profile of this SGLT2i as an adjunctive therapy to insulin. After a 26-week placebo-controlled randomized treatment phase, the >0.5% HbA_{1c} reduction with empagliflozin 10 and 25 mg is a clinically meaningful effect over intensified insulin. Furthermore, weight loss (up to −3.4 kg), increased glucose time in range (up to +3 h/day), and reductions in insulin need (up to −13%) and blood pressure (up to −3.9 mmHg for systolic) without increased severe hypoglycemia risk provide compelling evidence of clinical benefit for empagliflozin in T1D that, as with other SGLT2i agents (10–13), needs to be weighed against the increased DKA risk (14).

DKA incidence, based on the T1D Exchange clinic registry, is about 5% per year in adults (26). The increased DKA risk observed in the EASE program for the

Table 3—Adverse events

Event	EASE-2 and EASE-3 pooled			EASE-3	
	Empagliflozin 10 mg (*N* = 491)	Empagliflozin 25 mg (*N* = 489)	Placebo (*N* = 484)	Empagliflozin 2.5 mg (*N* = 241)	Placebo (*N* = 241)
Any adverse event	441 (89.8)	428 (87.5)	433 (89.5)	194 (80.5)	203 (84.2)
Drug-related adverse event	221 (45.0)	226 (46.2)	158 (32.6)	70 (29.0)	56 (23.2)
Adverse event leading to discontinuation	29 (5.9)	18 (3.7)	14 (2.9)	8 (3.3)	2 (0.8)
Serious adverse event	64 (13.0)	42 (8.6)	44 (9.1)	13 (5.4)	16 (6.6)
Death	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events of interest					
Event consistent with genital infection	63 (12.8)	70 (14.3)	21 (4.3)	13 (5.4)	6 (2.5)
Event consistent with urinary tract infection	47 (9.6)	41 (8.4)	41 (8.5)	13 (5.4)	11 (4.6)
Event consistent with volume depletion	12 (2.4)	16 (3.3)	8 (1.7)	1 (0.4)	3 (1.2)
Lower limb amputation	0	0	0	1 (0.4)	0
Bone fracture	14 (2.9)	5 (1.0)	8 (1.7)	5 (2.1)	2 (0.8)
Acute renal impairment	1 (0.2)	4 (0.8)	3 (0.6)	0	0
Hepatic event	8 (1.6)	8 (1.6)	7 (1.4)	1 (0.4)	1 (0.4)
Adjudicated ketoacidosis and ketosis					
Patients with certain ketoacidosis	21 (4.3)	16 (3.3)	6 (1.2)	2 (0.8)	3 (1.2)
Patients with >1 event	0	1	0	0	0
Number of events	21	18	6	2	3
Rate per 100 patient-years	5.94	5.05	1.77	1.65	2.52
Severity of event					
Severe events	2	6	1	0	1
Moderate events	13	8	4	0	1
Mild events	6	4	1	2	1
Outcome of event					
Sequelae	0	0	1	0	0
Fatal	0	1	0	0	0
Patients with potential ketoacidosis	15 (3.1)	13 (2.7)	6 (1.2)	3 (1.2)	1 (0.4)
Number of events	16	14	6	3	1
Number of mild events	16	14	6	3	1
Patients with ketosis	155 (31.6)	178 (36.4)	76 (15.7)	41 (17.0)	32 (13.3)
Patients with BHB ≥3.8 mmol/L*	21 (13.5)	17 (9.6)	4 (5.3)	7 (17.1)	2 (6.3)
Patients with cases adjudicated as unclassifiable	0	0	0	0	0
Adjudicated severe hypoglycemia					
Patients with any event	20 (4.1)	13 (2.7)	15 (3.1)	3 (1.2)	6 (2.5)
Number of events	33	14	21	9	6
Rate per 100 patient-years	9.54	4.02	6.35	7.66	5.22
Patients with fatal events	0	0	0	0	0
Patients with nocturnal events**	10	2	6	0	2

Data are *n* or *n* (%). Data are for patients who received at least one dose of a study drug and include events that occurred during treatment or within 7 days after the last receipt of a study drug. *Percentage of patients with BHB ≥3.8 mmol/L is calculated based on the number of patients with ketosis. **Onset between 0000 h and 0559 h.

higher doses is also reported similarly for sotagliflozin and dapagliflozin T1D programs (10,12). Although this risk appeared to be similar between the empagliflozin 10- and 25-mg doses, cases with more severe clinical characteristics, albeit very few in number, trended toward the 25-mg group. Interestingly, the observed comparable DKA risk between empagliflozin 2.5 mg and placebo suggests that lower SGLT2i doses conceivably may help to minimize this risk in T1D.

The approximate 0.3% HbA_{1c} reduction with empagliflozin 2.5 mg, although small in magnitude, is clinically relevant (27), especially when taking into consideration the totality of effects, including reductions in body weight, glucose variability, blood pressure, and the notably lower DKA risk. In addition to glucometabolic improvements, the HbA_{1c} effect of empagliflozin 2.5 mg comes without an increased risk of severe hypoglycemia, a risk observed with adjunct-to-insulin approaches using other drug classes (28–30).

Based on pharmacokinetic-pharmacodynamic modeling, increased urinary glucose excretion is observed in T1D versus T2D (15), suggesting differences in renal physiology and/or glucose handling (proposed model outlined in Supplementary Fig. 15). While glucosuria and glycemic benefits were observed in a 2-week dose-ranging T1D study of dapagliflozin, only the T2D-approved doses have been evaluated thus far in phase 3 trials (11,31). Our results suggest that the use of lower SGLT2i doses in T1D could achieve an optimal balance between safety and efficacy.

The challenges facing patients with T1D are perhaps best illustrated by data from the T1D Exchange clinic registry, which highlight the unmet need for adjunctive therapy to insulin to improve and facilitate T1D management. The overall mean HbA_{1c} was 8.4% and upwards of one-third of adult patients were overweight or obese, clinical characteristics that are similar to the EASE

populations at baseline (5). The 18-year follow-up data in the EDIC study further illustrate the need to address observed suboptimal glucose control and increased BMI (>28 kg/m^2) and obesity, a clear need in T1D patients that could be partially met with empagliflozin's benefits (4,32). Other than the increased DKA risk with 10- and 25-mg doses, empagliflozin's general safety profile in T1D patients was comparable to its safety profile as evaluated in >14,000 patients with T2D, with demonstrated risk reduction of cardiovascular death (−38%) and hospitalization for heart failure (−35%) in those with previous cardiovascular disease (16). Empagliflozin's cardiovascular and renal benefits continue to be evaluated in dedicated trials for heart failure (EMPagliflozin outcomE in Patients with chrOnic heaRt failure [EMPEROR]) and kidney disease (EMPA-KIDNEY), which are enrolling patients with T2D and T1D.

DKA risk correlated with concomitant illness or excessive insulin dose reductions (e.g., pump failure). This risk appears to be higher in female patients and with insulin pump use. If an SGLTi is to be considered in T1D, it should not be administered with a low carbohydrate diet and is not to be considered for people with history of excess alcohol intake or in case of a recent DKA episode. Adherence to optimized sick-day protocols irrespective of glucose levels, with emphasis on BHB measurements and temporary drug discontinuation in case of an infection or acute illness, should be implemented (33). The risk of DKA must be considered in the event of nonspecific symptoms (malaise, nausea, vomiting, anorexia, abdominal pain, and excessive thirst). Patients should be able to promptly assess ketones/BHB to enable early DKA detection/intervention in case of symptoms, regardless of glucose levels. If SGLT2i are to be used in clinical practice for T1D, additional educational guidance with self-monitoring of ketones/BHB will be necessary.

The EASE program overcame common limitations in the evaluation of SGLTi, such as short trial duration, lack of CGM data, and evaluation of a T1D-specific dose, but we acknowledge that the DKA mitigation strategies may not compare with those routinely used in current clinical practice. The lack of racial distribution and the assessment of the empagliflozin 2.5-mg dose in only one of the two phase 3 studies (up to 26 weeks) are regarded as limitations in this clinical program. An important aspect and strength of the EASE-2 and EASE-3 trials was that insulin intensification during the pretreatment optimization period and over the entire randomized treatment phase was based on local guidelines and investigator judgment as opposed to an enforced protocol-driven titration algorithm that is hard to replicate in clinical practice. The 6-week insulin intensification phase, which was based on real-world investigator-driven patient care, was effective and resulted in an approximate HbA_{1c} reduction of 0.5% across the two studies prior to the initiation of randomized therapy.

The totality of the EASE data, with adequate DKA risk mitigation and use of a lower (2.5 mg) dose than the doses approved for use in patients with T2D, appears to show a positive benefit-risk profile for empagliflozin in T1D. In this context, empagliflozin warrants further consideration at a lower dose as an adjunctive therapy to insulin as it is associated with clinically relevant glucometabolic improvements without an apparent increased risk of DKA and severe hypoglycemia in adults with T1D.

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