Boehringer Ingelheim

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE BRIEFING MATERIALS

EMPAGLIFLOZIN 2.5 MG TABLET

INDICATION: Adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes

OCTOBER 9, 2019

AVAILABLE FOR PUBLIC RELEASE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
Ridgefield, CT 06877-0368
(203) 798-9988

Note to the Reader

Boehringer Ingelheim (BI) has submitted a supplemental New Drug Application (NDA 204629) to the FDA proposing the use of empagliflozin 2.5 mg as adjunct treatment to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus. The proposed dose is lower than the currently approved doses for type 2 diabetes (i.e. empagliflozin 10 and 25 mg). This proposed type 1 diabetes-specific dose of empagliflozin 2.5 mg offers efficacy comparable to currently approved adjunct therapy (pramlintide), with a lower risk of diabetic ketoacidosis in comparison to higher doses.

This document provides background information for the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on 13 November 2019 to discuss the supplemental NDA. Sections 1 to 7 of the document summarize the design and outcome of the development program of empagliflozin in adult patients with type 1 diabetes mellitus. Additional in-depth information is provided in the Appendix (Section 8).

Executive Summary

Type 1 diabetes mellitus affects more than 1 million people in the U.S. and is associated with reduced life expectancy, reduction in quality of life and increased risk of complications. Patients with type 1 diabetes depend on the self-administration of exogenous insulin for survival, and self-monitoring of glucose multiple times a day to self-titrate insulin doses is integral to this.

Improved glycemic control in type 1 diabetes is expected to reduce the risk of long-term complications that place a morbidity and mortality burden on patients. This expectation is based on the correlation between the improvement of glucose control and the reduction of the risk of chronic complications in the NIH-led Diabetes Complications Control Trial (DCCT) and its ongoing follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study.

Despite advances in insulin formulations, delivery systems and glucose monitoring technologies, many patients are unable to achieve glycemic control. One key barrier to achieving individualized glycemic targets is the increased risk of hypoglycemia and weight gain associated with intensified insulin therapy. Novel treatment options that improve glycemic control without weight gain, and without increasing the risk for hypoglycemia, can help address this unmet need.

Drugs approved in type 2 diabetes have a large base of evidence. Multiple drugs for the treatment of type 2 diabetes have been evaluated as potential adjunct therapies for type 1 diabetes. SGLT2 inhibitors, a commonly used type 2 diabetes drug-class, have shown improved glycemic control in adults with type 1 diabetes without weight gain and without hypoglycemia. However, an increased risk of diabetic ketoacidosis (DKA), an inherent complication associated with type 1 diabetes, has been observed with SGLT2 inhibitors in patients with type 1 diabetes with doses approved or proposed for the treatment of type 2 diabetes.

Empagliflozin is an SGLT2 inhibitor that is approved at the doses of 10 mg and 25 mg for the treatment of adults with type 2 diabetes. It has a well-established efficacy and safety profile in this population.

Boehringer Ingelheim initially intended to register these doses for type 1 diabetes. The clinical development program was designed with this objective, and empagliflozin 10 mg and 25 mg were investigated in two Phase 3 trials.

In addition, a lower dose (empagliflozin 2.5 mg once daily) was investigated in one of the two Phase 3 trials based on the FDA's recommendation. The FDA noted *"safety concerns specific to patients with type 1 diabetes that may warrant exploration of a lower dose"*. The agency also highlighted that *"we expect that the risk/benefit in this population will be different than in the type 2 diabetes population and are uncertain that doses approved for type 2 diabetes are optimal for type 1 diabetes"*.

Within the context of these two Phase 3 trials incorporating risk reduction measures for DKA, all three empagliflozin doses showed a positive benefit-risk profile. However, the 2.5 mg dose emerged with the most favorable profile for patients with type 1 diabetes, with a lower risk of DKA compared with the higher doses.

Empagliflozin 2.5 mg yielded:

- HbA_{1c} reductions in the range of 0.3%, comparable to the only approved adjunct therapy for type 1 diabetes in the U.S. (pramlintide)
- Reductions in body weight (-1.8 kg) and systolic blood pressure (-2.1 mmHg)
- No increased risk of hypoglycemia
- Improved patient satisfaction with treatment as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ)

Phase 3 results for empagliflozin 2.5 mg are consistent with two randomized controlled Phase 2 trials. Since the empagliflozin 2.5 mg dose was studied in only one of the Phase 3 trials, the effect of this dose was simulated in the other Phase 3 trial based on exposure-response analyses. These exposure-response studies demonstrated consistency of treatment the effect with the data from the three randomized clinical trials that studied the 2.5 mg dose.

While treatment with empagliflozin 2.5 mg was not associated with an increase in the observed rate of DKA as compared with placebo in clinical trial settings, a potential increased risk in the real-world setting cannot be ruled out. Boehringer Ingelheim therefore proposes a package of measures in the post-marketing setting, based on the measures employed in the clinical trial program. Dose-selection is an important element in mitigating the risk of DKA in this context.

The totality of data has led to the conclusion that empagliflozin 2.5 mg has the potential to be a treatment option for appropriate patients living with type 1 diabetes. Treatment with empagliflozin 2.5 mg can potentially address the unmet need of these patients to improve glycemic control without weight gain and without an increase in hypoglycemia.

Therefore, Boehringer Ingelheim proposes to register empagliflozin 2.5 mg as a specific dose for the treatment of adults with type 1 diabetes as an adjunct to insulin therapy.

This type 1 diabetes-specific dose of empagliflozin 2.5 mg is proposed to be marketed under a type 1 diabetes standalone brand which is distinct from the brand for empagliflozin currently approved for type 2 diabetes. This will enable healthcare providers and patients to be provided with type 1 diabetes-specific prescribing information and focused education.

A post-marketing study is proposed to further assess the safety of empagliflozin 2.5 mg, including the risk of DKA, in patients with type 1 diabetes in routine clinical practice setting.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
ADA	American Diabetes Association
AESI	Adverse event of special interest (protocol-defined)
ANCOVA	Analysis of covariance
BHB	Beta-hydroxybutyrate
BI	Boehringer Ingelheim
BMI	Body mass index
CEC	Clinical Event Committee
CGM	Continuous glucose monitoring
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DTSQs/c	Diabetes Treatment Satisfaction Questionnaire status/change version
EASD	European Association for the Study of Diabetes
EASE	Empagliflozin as Adjunctive to InSulin thErapy
eGFR	(Estimated) glomerular filtration rate
EDIC	Epidemiology of Diabetes Control and Complications
eGFR	Estimated glomerular filtration rate
Empa	Empagliflozin
FAS	Full analysis set
FDA	Food and Drug Administration
HbA_{1c}	Glycated hemoglobin
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IQR	Interquartile range
MAGE	Mean amplitude of glycemic excursions

MDI	Multiple daily injections
mITT	Modified intention-to-treat
MMRM	Mixed model for repeated measures
NDA	New Drug Application
OC	Observed cases (for analysis of on-treatment data)
OC-P	Observed cases excluding data after use of paracetamol
OC-H	Observed cases excluding data after use of antihypertensives
OC-AD	Observed cases including data after treatment discontinuation (for analysis of on-treatment and off-treatment data)
OR	Original results
PD	Pharmacodynamics
PG	Plasma glucose
PK	Pharmacokinetics
PRO	Patient-reported outcome
PT	Preferred term
PY	Patient-year
RCT	Randomized controlled trial
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT	Sodium-glucose co-transporter
T1D	Type 1 diabetes
TDID	Total daily insulin dose
UGE	Urinary glucose excretion

1. Introduction

New treatment options are needed to ease the burden of patients with type 1 diabetes

Type 1 diabetes mellitus is a lifelong disease of autoimmune origin that affects more than 1 million people in the U.S (1, 2). It is associated with reduced life expectancy and chronic complications (3-6). The NIH-led Diabetes Complications Control Trial (DCCT) and its follow-up, Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated risk reduction for the chronic complications in patients who achieve better glucose control (6-8). Improving the management of type 1 diabetes and addressing its complication risks continues to be a priority for affected individuals and for healthcare providers and patient advocacy groups.

Glycated hemoglobin (HbA_{1c}) is the commonly employed marker of glycemic control, with targets ideally set on a personalized basis through consultation between the patient and the healthcare provider. The American Diabetes Association (ADA) recommends HbA_{1c} <7% as a reasonable HbA_{1c} goal for many adults (9).

All patients with type 1 diabetes require administration of insulin. Attaining and sustaining HbA_{1c} targets with insulin optimization remains a challenge. 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 (5, 10-12). The recent Type 1 Diabetes Exchange Registry data from specialty clinics in the U.S. showed that the mean HbA_{1c} in a broad population was 8.4% and that more than 50% of the adult patients were overweight or obese (10). Moreover, severe hypoglycemia continues to be an important safety concern in the treatment of patients with type 1 diabetes (10).

Adjunct to insulin treatment options for patients with type 1 diabetes are currently limited. The only marketed adjunct to insulin therapy in the U.S. is pramlintide, an injectable medication that is administered with each major meal. While placebo-corrected HbA_{1c} reductions in the range of 0.25 to 0.34% and weight reduction in the range of 1.5 to 2 kg were reported in clinical trials, pramlintide is associated with an increased risk of severe hypoglycemia, and is not widely used (13).

New adjunct treatments should aim to provide glycemic benefits in type 1 diabetes without increasing risks of weight gain and hypoglycemia

Drugs approved in type 2 diabetes have a large base of evidence and provide opportunities to be repurposed as adjunct therapies for type 1 diabetes to complement insulin.

SGLT2 inhibitors, a commonly used drug class for the treatment of type 2 diabetes, increase urinary glucose excretion by reducing renal re-absorption of glucose. This results in the reduction of blood glucose levels, and HbA1c. Based on studies in patients with type 1 diabetes, improvements of gluco-metabolic parameters have been established including placebo-corrected HbA1c reductions observed in the range of 0.3 to 0.5% and body weight reductions in the range of

2 to 4 kg following 6 months of treatment (14). In randomized controlled trials in patients with type 1 diabetes, the risk of hypoglycemia with SGLT inhibitor use was not increased relative to placebo, reflecting its mechanism of action.

Increased diabetic ketoacidosis (DKA) risk is included in the current product labels of all SGLT2 inhibitors approved for type 2 diabetes based on post-marketing reported DKA cases for this class of drugs and owing to their potential to induce ketogenesis through several pathophysiological mechanisms (15, 16).

In addition, an increased risk of DKA has been observed with multiple SGLT2 inhibitors in patients with type 1 diabetes (17). In many cases with use of SGLT2 inhibitors in type 1 diabetes, DKA occurred with lower than typically observed glucose levels (18). This atypical presentation of DKA can make the clinical diagnosis of this serious complication more challenging.

Therefore, DKA risk was systematically evaluated in the empagliflozin type 1 diabetes (EASE) program.

Boehringer Ingelheim proposes a type 1 diabetes-specific dose of the SGLT2 inhibitor empagliflozin as adjunctive to insulin treatment

Empagliflozin is an SGLT2 inhibitor that is currently approved at the doses of 10 mg and 25 mg for the treatment of type 2 diabetes.

Empagliflozin is currently indicated in the U.S.:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

In addition to the U.S., empagliflozin is approved in 100 other countries, with more than 7 million patient-years of exposure.

Boehringer Ingelheim initially intended to develop and seek registration for the 10 and 25 mg doses for type 1 diabetes. The clinical development program in type 1 diabetes was designed with this objective. Only these two doses were therefore included in the initial Phase 3 planning.

During Phase 3 planning, FDA recommended exploration of an additional lower dose. FDA stated that *"there are safety concerns specific to type 1 diabetes patients that may warrant exploration of a lower dose. We expect that the risk/benefit in this population will be different than in the type 2 diabetes population and are uncertain that doses approved for type 2 diabetes are optimal for type 1 diabetes."* (Type C Meeting, Written Responses 11/07/2014).

Subsequently, empagliflozin 2.5 mg was included in one of the two Phase 3 studies. The 2.5 mg dose was selected based on Phase 2 data that showed that its exposure-response characteristics

were well differentiated from the 10 mg dose. In the Phase 2 EASE-1 trial, empagliflozin 2.5 mg provided 70% of the urinary glucose excretion (UGE) effect of the higher doses (see Section 3.6, Figure 11).

The results of the EASE Phase 3 trials showed that the 2.5 mg dose had an efficacy profile comparable to the only adjunct therapy approved for type 1 diabetes in the U.S. (pramlintide). The results from the EASE-3 study were also consistent with results from two Phase 2 studies that included an empagliflozin 2.5 mg dose.

The 2.5 mg dose of empagliflozin was only evaluated in one of the two Phase 3 trials. Therefore, exposure-response simulation studies were conducted to address whether the effect of empagliflozin 2.5 mg would be confirmed in the trial that did not include this dose.

Crucially, the 2.5 mg dose was associated with an observed lower risk of DKA than the higher doses. Meanwhile, data from other type 1 diabetes trials with SGLT inhibitors also showed an increased risk of DKA when using type 2 diabetes doses (17). Taken together, the totality of data highlights the importance of dose-selection as a critical element in mitigating the risk of DKA in the context of SGLT2 inhibitor therapy in type 1 diabetes.

2. The EASE Program: Investigation of empagliflozin in type 1 diabetes

2.1 Overview of the EASE program

The EASE (Empagliflozin as Adjunctive to inSulin thErapy) Phase 3 program in patients with type 1 diabetes included two international, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials of once-daily oral empagliflozin doses conducted over 26 weeks (EASE-3) and 52 weeks (EASE-2).

EASE-3 investigated empagliflozin 2.5, 10, and 25 mg over 26 weeks. EASE-2 investigated empagliflozin 10 and 25 mg over 52 weeks. (Table 1).

The assessment of empagliflozin in the Phase 3 trials is complemented by two randomized, placebo-controlled Phase 2 trials, EASE-1 (performed in Caucasian patients) and J-EASE-1 (performed in Japanese patients). Both trials tested the 2.5, 10 and 25 mg doses.

As empagliflozin 2.5 mg emerged as a viable therapeutic option at the end of Phase 3, exposure-response simulation studies were performed to simulate the time course of HbA1c lowering for this dose up to 52 weeks in the EASE-2 trial population. The simulations were performed independently of the data from EASE-3.

The totality of these data support the proposed indication of empagliflozin 2.5 mg as adjunct to insulin in patients with type 1 diabetes.

Table 1 Overview of the EASE program

Phase	Study	Duration	Treated patients			
			Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg
Phase 3	EASE-3	26 weeks	241	241	248	245
	EASE-2	52 weeks	243	--	243	244
Phase 2	EASE-1	4 weeks	19	19	19	18
	J-EASE-1	4 weeks	11	13	12	12
Exposure-response simulation study	EASE-2 simulation	52 weeks	239[1]	239[1]	--	--

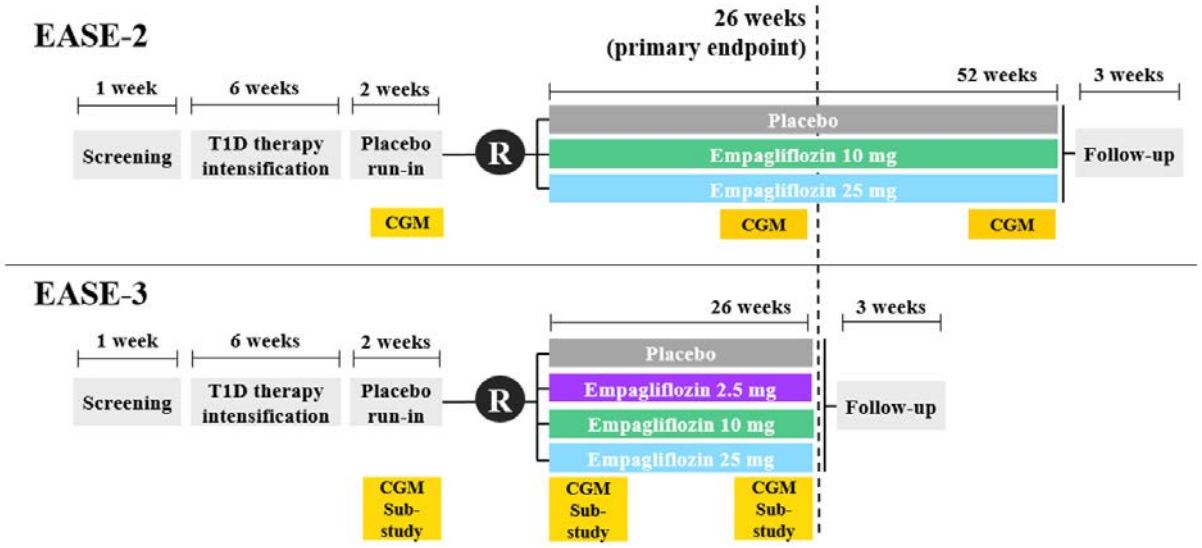
1 Number of simulated patients (n=500 trials)

2.2 Phase 3 trial design

EASE-2 and EASE-3 were randomized double-blind placebo-controlled trials. The trials included 310 sites mainly from North America and Europe. The main objective was to evaluate the safety and efficacy of empagliflozin (10 and 25 mg doses plus the lower dose of 2.5 mg) as adjunct to intensified insulin in patients with type 1 diabetes.

The design and conduct of the two studies were identical except for the following differences in EASE-3: the inclusion of empagliflozin 2.5 mg, a shorter treatment duration, and the assessment of continuous glucose monitoring as a substudy (Figure 1).

Figure 1 EASE Phase 3 trial design



CGM: continuous glucose monitoring; R: randomization

A treatment approach consistent with current clinical practice

The treatment period was preceded by a 6-week lead-in insulin intensification period, a 2-week placebo run-in period, and followed by a 3-week safety follow-up. The insulin intensification period had the aim of optimizing each participant's insulin dose regimen driven by the study investigator and in accordance with local guidelines. Adjustments to insulin therapy could be implemented throughout the study based on investigator judgement to aim for the best standard of care.

Primary endpoint

The primary endpoint in the Phase 3 trials was the change from baseline in HbA_{1c} at Week 26.

Selection of HbA_{1c} was made in line with FDA guidance, stating that for purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA_{1c} (19).

Clinical endpoints beyond HbA_{1c}

Several outcomes beyond HbA_{1c} with clinical relevance for patients with type 1 diabetes were evaluated, based on FDA recommendation. These were designated as 'key secondary endpoints` estimating the change from baseline at Week 26 in:

- Body weight
- Continuous glucose monitoring (CGM) parameters - EASE-2 only
- Total daily insulin dose
- Systolic blood pressure
- Diastolic blood pressure
- Symptomatic hypoglycemic adverse events (AEs) with blood glucose <54 mg/dL and/or severe hypoglycemia

CGM parameters such as time in range and interquartile range were assessed as key secondary endpoints in EASE-2. However, these parameters were also evaluated in EASE-3 as a substudy. Further details on the key secondary endpoints are provided in Section 8.2.1.

The primary efficacy analysis of the primary endpoint included on-treatment data only (Full Analysis Set of patients, FAS). In addition, an effectiveness analysis, including on- and off-treatment data, was performed in a hierarchical manner (modified intention-to-treat set of patients, mITT). Confirmatory testing of the key secondary endpoints was performed for the 10 mg and 25 mg doses. For the empagliflozin 2.5 mg dose, only the primary efficacy analysis of the primary endpoint was confirmatory, reflecting the initial intent of the clinical development program to register only the higher doses. All other analyses for the 2.5 mg dose are therefore descriptive (see Section 8.2.1 for further details).

The efficacy analysis was chosen as the primary analysis based on clinical practice. Physicians and their patients are primarily interested in the expected individual therapeutic effects for an adherent (on-treatment) patient. The effectiveness estimate combines information from adherent and non-adherent (on- and off-treatment) patients into one estimate for the entire population. However, the results of the efficacy analysis and the effectiveness analysis were very similar, since the discontinuation rate was low in the Phase 3 trials (7% discontinuation rate for empagliflozin 2.5 mg in EASE-3).

The EASE program aimed to study a population representative of current U.S. patients

In EASE-2, 730 patients were treated and 723 of these were included in the full analysis set. In EASE-3, 975 patients were treated and 961 were included in the full analysis set. There was a high rate of treatment completion in both trials. About 90% of patients completed treatment up to Week 26 in both trials and 85% completed treatment up to Week 52 (EASE-2); see Section 8.5.1 for more details on patient disposition.

Baseline characteristics of patients were consistent with the inclusion/exclusion parameters of the trials (Table 2) and were balanced between the treatment groups (Section 8.5.2.1). A high mean body mass index was observed in the trial population (28 kg/m² in EASE-3). More than half of patients had HbA_{1c} of at least 8% at baseline. This reflects the general trend for overweight and obesity in the type 1 diabetes population and challenges to achieve glycemic targets (5, 10-12).

Baseline characteristics were generally balanced between U.S. patients and non-U.S. patients. More pump use was noted in the U.S. population (about 60% pump users) versus non-U.S. patients (about 30% pump users). Overall, baseline characteristics of U.S. patients were comparable with data reported from the Type 1 Diabetes Exchange Registry and data from observational studies in the U.S. (10, 20-23).

Table 2 Baseline characteristics of patients in the Phase 3 trials – full analysis set of patients

Baseline parameter	EASE-3	EASE-2
Number of patients, N (100%)	961	723
Sex, N (%)		
Male	469 (48.8)	338 (46.7)
Female	492 (51.2)	385 (53.3)
Main regions, N (%)		
Europe	602 (62.6)	394 (54.5)
North America	244 (25.4)	280 (38.7)
Other	115 (12.0)	49 (6.8)
Race (incl. combinations), N (%)		
White	916 (95.3)	682 (94.3)
Black/African American	23 (2.4)	18 (2.5)
Asian	12 (1.2)	24 (3.3)
Other	14 (1.5)	1 (0.1)
Age [years], mean (SD)	43.1 (13.5)	45.2 (13.3)
Blood pressure [mmHg], mean SBP/DBP	124/76	125/76
BMI [kg/m^2], mean (SD)	28.23 (5.05)	29.18 (5.65)
eGFR[1] [mL/min/1.73m^2], mean (SD)	96.83 (19.71)	94.99 (18.47)
≥90, N (%)	645 (67.1)	462 (63.9)
60 to <90, N (%)	274 (28.5)	238 (32.9)
<60, N (%)	42 (4.4)	23 (3.2)
Time since diagnosis of type 1 diabetes [years] (SD)	21.0 (12.1)	22.6 (12.7)
Mean HbA_{1c} [%]	8.18 (0.62)	8.10 (0.57)
<8.0, N (%)	403 (41.9)	322 (44.5)
≥8.0, N (%)	558 (58.1)	401 (55.5)
Daily insulin dose [U/kg], mean (range)	0.70 (0.5–1.7)	0.71 (0.1–1.9)
Type of insulin therapy, N (%)		
MDI	636 (66.2)	429 (59.3)
Insulin pump	325 (33.8)	294 (40.7)

SD: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, eGFR: estimated glomerular filtration rate, MDI: multiple daily injections
1 Based on CKD−EPI creatinine formula

3. Empagliflozin 2.5 mg efficacy comparable to currently approved adjunct therapy

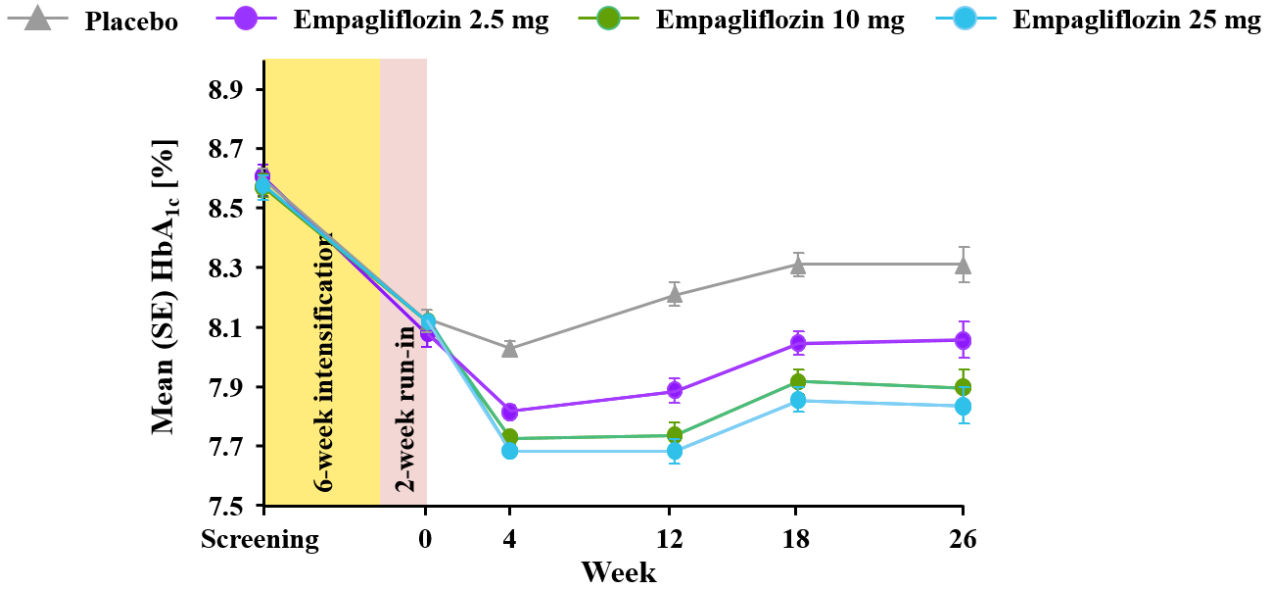
This section focuses mainly on the results of empagliflozin 2.5 mg in the EASE-3 trial. A brief overview of efficacy results of EASE-2 is also provided, with further details presented in Section 8.6.2.

Boehringer Ingelheim is not seeking an indication in type 1 diabetes for the 10 mg and 25 mg doses; data of these doses are presented to support establishing a dose-response relationship for efficacy and safety in patients with type 1 diabetes.

3.1 Reduction in HbA_{1c} with empagliflozin 2.5 mg

Prior to randomization, patients had their insulin therapy intensified per standard of care. As a result, HbA_{1c} was reduced by approximately 0.5% following this period (Figure 2). During randomized treatment, HbA_{1c} gradually increased in all treatment groups after weeks 4 to 12. This gradual increase was expected and reflects the clinical challenge for patients to maintain the initial high level of engagement with diet, exercise, and glucose monitoring over an extended period.

Figure 2 HbA_{1c} over time in EASE-3



Patients with data at visit						
Placebo	238	238	236	227	222	217
Empagliflozin 2.5 mg	237	237	237	234	228	225
Empagliflozin 10 mg	244	244	243	234	225	225
Empagliflozin 25 mg	242	242	241	231	226	221

Empagliflozin provided clinically meaningful and statistically significant HbA_{1c} reductions versus placebo at Week 26 that were not achieved with insulin alone. The primary efficacy analysis (based on the FAS, with adjustment for multiple testing) showed changes from baseline versus placebo of:

- **-0.28% (99% CI -0.46, -0.11) for empagliflozin 2.5 mg**
- -0.45% (97.5% CI -0.60, -0.30) for empagliflozin 10 mg
- -0.52% (97.5% CI -0.68, -0.37) for empagliflozin 25 mg.

Results of the effectiveness analysis (modified intention-to-treat set of patients) were almost identical (Figure 3). Pre-specified sensitivity analyses with alternative methods to impute missing HbA_{1c} values included:

- A multiple imputation approach, using the observed off-treatment values within the respective treatment group as basis for multiple imputations of missing data after treatment discontinuation.
- A pattern-mixture-model with a 'jump to reference' approach, using multiple imputations based on observed data in the placebo group.

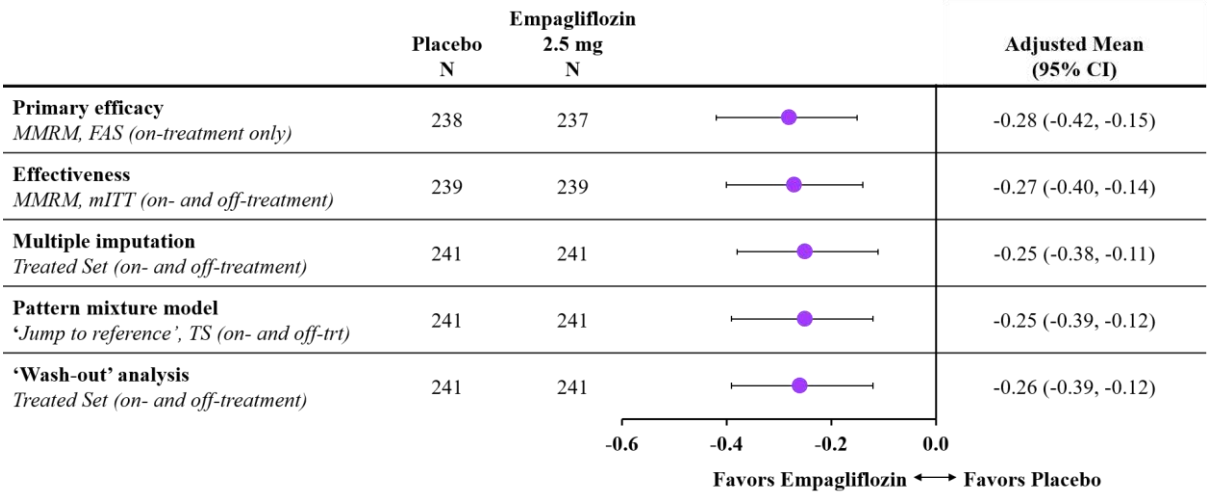
In addition, a 'wash-out' analysis was performed, as requested by the FDA during review of the submission package:

- A multiple imputation approach, using the observed data at Week 26 from completers in the placebo group as basis for multiple imputations of missing data at Week 26.

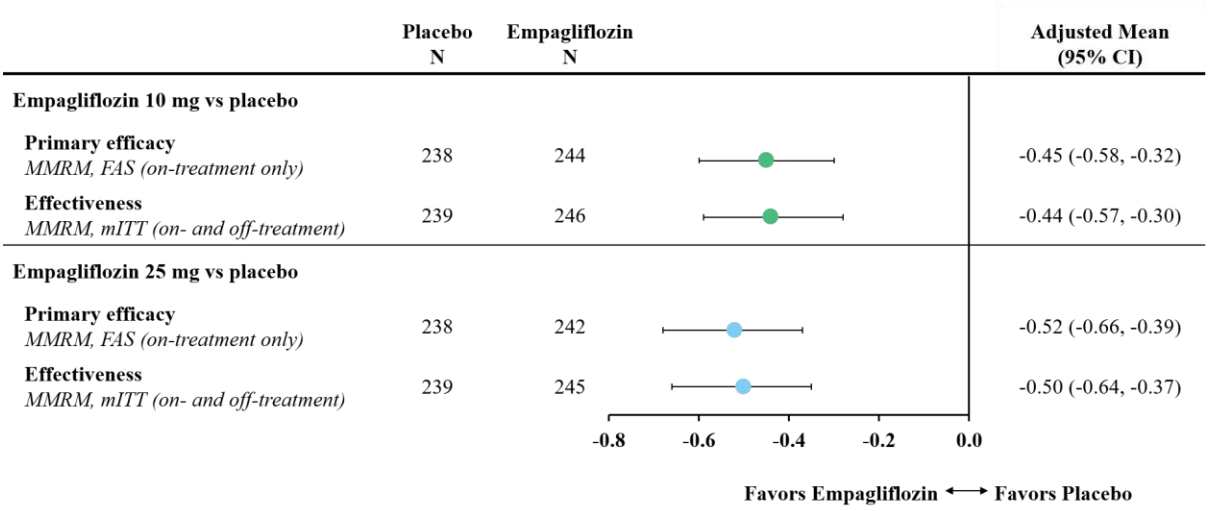
Consistent results for empagliflozin 2.5 mg were observed across all of these sensitivity analyses (comparing adjusted means and 95% CIs); see Figure 3.

Figure 3 Change from baseline in HbA_{1c} [%] at Week 26 in EASE-3

Empagliflozin 2.5 mg versus placebo



Empagliflozin 10 mg and 25 mg versus placebo



FAS: full analysis set, mITT: modified intention-to-treat set, MMRM: mixed-effect model for repeated measures

Subgroup analyses

Consistent results for the primary analysis were observed across subgroups in the Phase 3 trials, with the exception of patients with eGFR <60 mL/min/1.73m^2 (Figure 4), despite a non-significant treatment-by subgroup interaction (p=0.17). This subgroup (7 patients analyzed for empagliflozin 2.5 mg) showed a change from baseline in HbA_{1c} versus placebo of 0.09 (95% CI -0.59, 0.78) for empagliflozin 2.5 mg. Similar results were observed for empagliflozin 10 mg and 25 mg for this subgroup (see Section 8.6.1.1). Based on these data, and a mechanistic linkage between renal

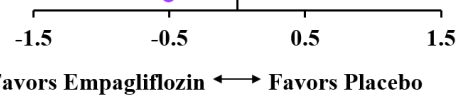
function and glycemic control for SGLT2 inhibitors, empagliflozin 2.5 mg would not be recommended in this population.

For the subgroups based on the time elapsed since diagnosis of type 1 diabetes, a treatment-by subgroup interaction at the 10% level was observed (p=0.07). For empagliflozin 2.5 mg, the change from baseline in HbA_{1c} versus placebo was -0.81 (95% CI -1.36, -0.26) in patients with no more than 5 years since diagnosis. However, this result is based on a very low number of patients and no clear differences were observed for the 10 mg and 25 mg doses for this subgroup parameter (see Section 8.6.1.1). Overall, the data support a conclusion that time since diagnosis has no relevant impact on HbA_{1c} reduction under empagliflozin treatment in patients with type 1 diabetes.

Patients with baseline HbA_{1c} >8% showed a more pronounced reduction of HbA_{1c} as compared with the overall trial population. The reduction was -0.33% in patients with a baseline value of 8% to <9 % and -0.51% in patients with a baseline value of at least 9% (Figure 4). This is of clinical relevance in the U.S., as mean HbA_{1c} is above 8% across a large segment of the type 1 diabetes population (10).

Figure 4 Change from baseline in HbA_{1c} at Week 26 by subgroup for empagliflozin 2.5 mg in EASE-3

		n Analyzed	Difference (95% CI)
Empagliflozin 2.5 mg vs placebo		225/217	-0.28 (-0.42, -0.15)
Region	**US**	40/36	-0.32 (-0.63, -0.01)
	Non-US	185/181	-0.28 (-0.42, -0.13)
Sex	**Female**	114/115	-0.17 (-0.35, 0.01)
	Male	111/102	-0.41 (-0.60, -0.22)
Age	**<30**	46/44	-0.25 (-0.54, 0.04)
	30-<45	76/78	-0.36 (-0.58, -0.14)
	45 to <65	86/83	-0.19 (-0.41, 0.02)
	≥65	17/12	-0.44 (-0.96, 0.09)
BMI	**<25 kg/m²**	57/65	-0.12 (-0.37, 0.13)
	25-<30 kg/m²	96/91	-0.43 (-0.64, -0.23)
	≥30 kg/m²	72/61	-0.21 (-0.45, 0.03)
Time since diagnosis	**≤5 years**	14/11	-0.81 (-1.36, -0.26)
	>5-10 years	23/30	-0.26 (-0.64, 0.12)
	>10-25 years	106/91	-0.30 (-0.50, -0.10)
	>25 years	82/85	-0.19 (-0.41, 0.03)
Insulin administration	**Multiple daily injections**	148/141	-0.32 (-0.49, -0.16)
	Insulin pump	77/76	-0.21 (-0.43, 0.02)
Insulin dose	**<0.5 U/kg**	34/38	-0.18 (-0.51, 0.15)
	0.5-0.8 U/kg	129/101	-0.22 (-0.41, -0.04)
	>0.8 U/kg	50/64	-0.43 (-0.69, -0.17)
eGFR	**≥90 ml/min**	152/154	-0.28 (-0.44, -0.12)
	60-<90 ml/min	57/46	-0.32 (-0.59, -0.05)
	<60 ml/min	10/7	0.09 (-0.59, 0.78)
HbA_{1c}	**<8.0**	94/94	-0.18 (-0.38, 0.03)
	8.0 to <9.0	110/99	-0.33 (-0.52, -0.13)
	≥9.0	21/24	-0.51 (-0.93, -0.10)



Pre-defined subgroup analyses
BMI: body mass index, eGFR: estimated glomerular filtration rate

3.2 Gluco-metabolic improvements beyond HbA_{1c} with empagliflozin 2.5 mg

The benefits of treatment with empagliflozin beyond a reduction in HbA_{1c} were investigated. Outcomes beyond HbA_{1c}, such as reduction in body weight, time in range and systolic blood pressure, were selected since they are highly relevant for patients living with type 1 diabetes as discussed at workshops such as the "Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c)" public workshop sponsored by the FDA Center for Drug Evaluation and Research (24).

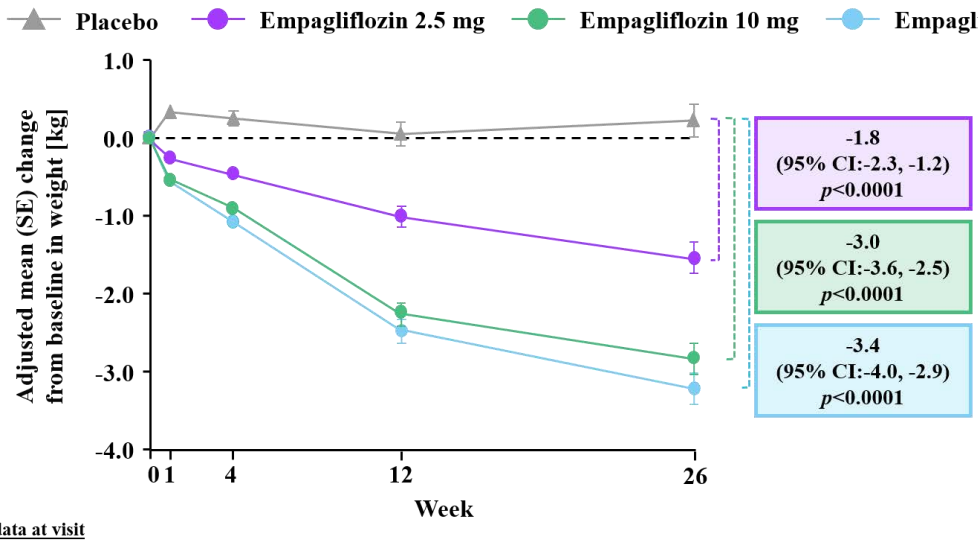
The results for the EASE-3 trial are described below. Secondary endpoints for the empagliflozin 2.5 mg dose were pre-specified, although not included in the hierarchical testing.

Consistent results were observed in EASE-2 for empagliflozin 10 mg and 25 mg, with effects generally sustained up to 52 weeks (Section 8.6.2.2).

Reduction in body weight

Empagliflozin 2.5 mg was associated with a placebo-corrected reduction of 1.8 kg (95% CI -2.3, -1.2), p<0.0001. There was a dose-dependent decrease in body weight up to Week 26 in the empagliflozin treatment groups, while body weight in the placebo group remained stable over time (Figure 5).

Figure 5 Change from baseline in body weight over time in EASE-3



Patients with data at visit					
Placebo	238	232	237	227	219
Empagliflozin 2.5 mg	237	234	236	233	223
Empagliflozin 10 mg	243	239	242	233	225
Empagliflozin 25 mg	240	239	237	231	223

Confirmatory analysis for empagliflozin 10 and 25 mg, exploratory analysis for empagliflozin 2.5 mg; MMRM, FAS (on treatment)

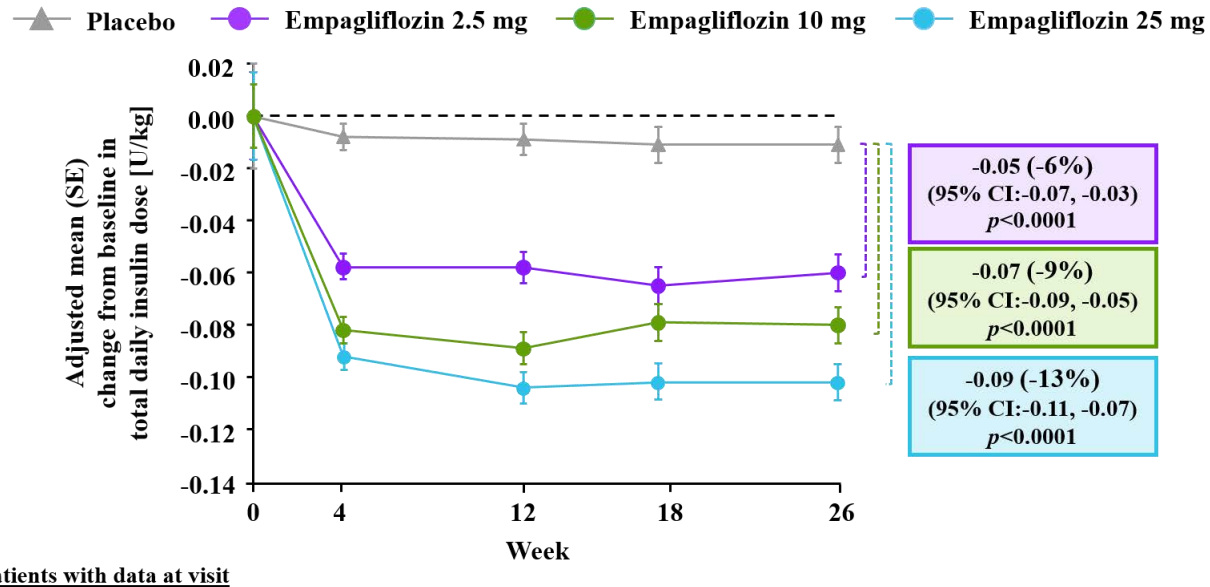
Reduction in insulin dose

A dose-dependent reduction in insulin dose was demonstrated, with a reduction of 6% with empagliflozin 2.5 mg and up to 13% with empagliflozin 25 mg after 26 weeks. The reductions in basal and bolus insulin doses were evenly distributed (data not shown). These results are important also from a safety perspective, because insulin dose reduction itself is a known risk factor for DKA.

The need to reduce insulin dose when initiating empagliflozin occurred shortly after the start of therapy. The total daily insulin dose was largely stabilized by Week 4 of treatment as assessed by patient-reported insulin doses.

Importantly, the total daily insulin dose in patients assigned to placebo was relatively stable over the entire treatment period and comparable to the levels reported at randomization (Figure 6).

Figure 6 Change from baseline in total daily insulin dose over time in EASE-3



Patients with data at visit

Placebo	217	217	201	196	189
Empagliflozin 2.5 mg	223	222	208	202	189
Empagliflozin 10 mg	217	215	195	187	177
Empagliflozin 25 mg	220	218	206	195	187

Confirmatory analysis for empagliflozin 10 ad 25 mg, exploratory analysis for empagliflozin 2.5 mg; MMRM, FAS (on treatment)

Reduction in blood pressure

Systolic blood pressure was reduced in all empagliflozin groups. The mean reduction versus placebo at Week 26 in EASE-3 was:

- **-2.1 mmHg (95% CI -3.9, -0.2), p=0.027 for empagliflozin 2.5 mg (exploratory analysis)**
- -3.9 mmHg (95% CI -5.7, -2.1), p<0.0001 for empagliflozin 10 mg (confirmatory analysis)
- -3.7 mmHg (95% CI -5.6, -1.9), p<0.0001 for empagliflozin 25 mg (confirmatory analysis)

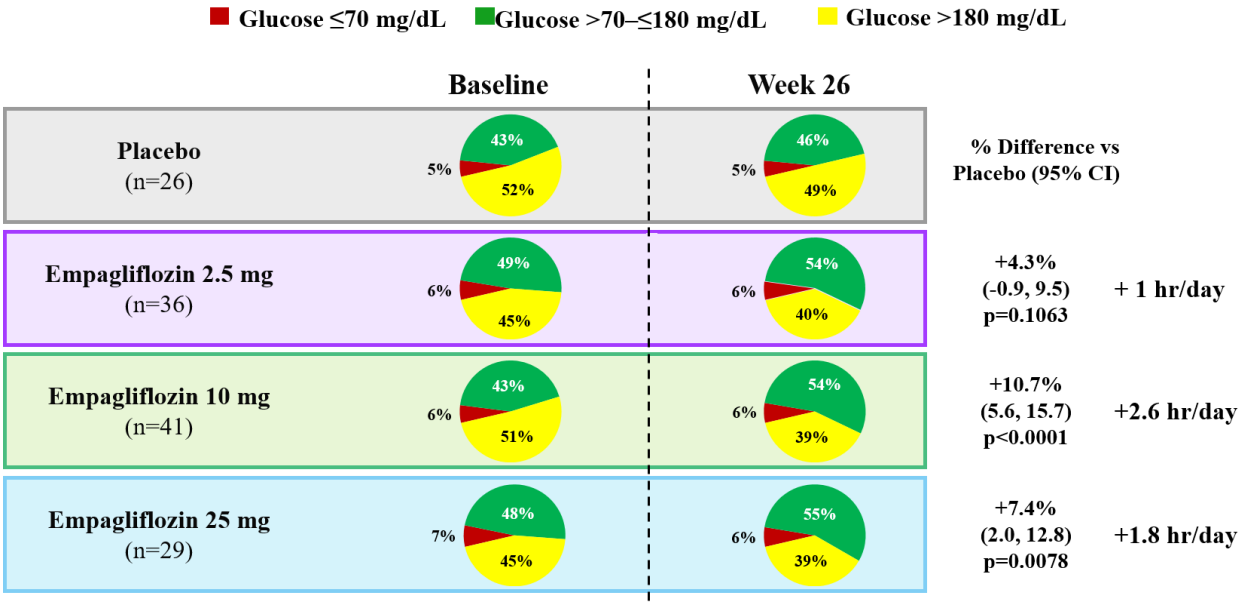
See Section 8.6.1.2 for more details. Given the high risk of cardiovascular and renal disease, the empagliflozin-mediated reduction in blood pressure might be also beneficial in patients with type 1 diabetes.

Increase in time spent in normal glucose range

The analysis of continuous glucose monitoring (CGM) showed that the time the patients spent in the normal glucose range (>70 to 180 mg/dL) increased by about 1 hour per day with empagliflozin 2.5 mg in EASE-3 (Figure 7 and Section 8.6.1.3). This positive effect was mainly

driven by a reduction of time spent in hyperglycemia, with no significant changes in time spent in hypoglycemia.

Figure 7 Change from baseline in the time spent in the target glucose range in EASE-3



The CGM parameter time in range was analyzed within a substudy in EASE-3 in 17% of the patients, and was not powered for empagliflozin 2.5 mg nor the higher doses. The results from this substudy were consistent with those in EASE-2, where CGM was analyzed in all patients as a key secondary endpoint (Sections 3.5 and 8.6.2.2).

Although the increase in time spent in target glucose range was not statistically significant for empagliflozin 2.5 mg, the observed mean increase of 1 hour per day can be of clinical relevance for patients. Improvement of time in range represents a reduction of the undesirable glucose excursions.

3.3 No increase in hypoglycemia with empagliflozin 2.5 mg

Three pre-specified analyses of hypoglycemia were performed for the Phase 3 trials:

- The rate of investigator-reported symptomatic hypoglycemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycemic events (Key secondary efficacy endpoint of hypoglycemia)
- Severe hypoglycemia (adjudicated safety endpoint)
- Patient-reported hypoglycemia (patient-reported safety endpoint)

Further details are provided in Section 8.6.3.

The key secondary efficacy endpoint of hypoglycemia will be presented separately for EASE-2 and EASE-3. For the other two safety endpoints of hypoglycemia, empagliflozin 2.5 mg was compared with placebo in the EASE-3 trial, while the 10 mg and 25 mg doses were analyzed pooled across both Phase 3 trials. This was the general approach for the safety data in Phase 3 (see Section 4).

Key secondary endpoint of hypoglycemia

The key secondary endpoint for hypoglycemia was the rate of investigator-reported symptomatic hypoglycemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycemic events.

No significant treatment difference was observed between empagliflozin 2.5 mg and placebo (Figure 8).

Severe hypoglycemia

Severe hypoglycemic events were those requiring external assistance for recovery and were adjudicated by an independent clinical endpoint committee. These events represent the most severe presentation of hypoglycemia and a life-threatening complication in patients with type 1 diabetes. They are categorized as Level-3 events by the International Hypoglycemia Study Group (25).

Empagliflozin 2.5 mg did not increase the risk of severe hypoglycemia (Figure 8).

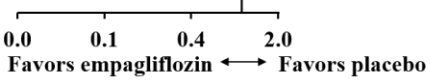
Patient-reported hypoglycemia

The broadest analysis of hypoglycemia was based on all patient-reported events with blood glucose <54 mg/dL, as captured by an electronic diary. This analysis was pre-specified during the conduct of the Phase 3 trials upon publication of the position statement from the International Hypoglycemia Study Group (25). These events represent serious and clinically important events and are categorized as Level-2 events by the International Hypoglycemia Study Group.

The results show a trend towards a reduced rate with empagliflozin 2.5 mg versus placebo (Figure 8).

Figure 8 Hypoglycemia results for empagliflozin 2.5 mg

	Empagliflozin		Placebo			
	N	Events, n	N	Events, n	Rate Ratio (95% CI)	p-value
Key secondary hypoglycemia endpoint[1]						
Empagliflozin 2.5 mg	237	976	238	1339	0.93 (0.68, 1.27)	0.6587
Severe hypoglycemia		*Patients/ Events*		*Patients/ Events*		
Empagliflozin 2.5 mg	241	3/9[2]	241	6/6	0.18 (0.03, 1.15)	0.0698
Patient-reported[3] hypos with BG <54 mg/dL						
Empagliflozin 2.5 mg	241	2531	241	2976	0.83 (0.67, 1.04)	0.0978



Negative binomial model; BG: blood glucose

1 Rate of investigator-reported symptomatic hypoglycemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycemic events –exploratory analysis - FAS (on treatment), model including baseline hypoglycemia

2 One patient on empagliflozin 2.5 mg experienced 6 severe hypoglycemia events pre-randomization and 7 events post-randomization – exploratory analysis - treated set, model including baseline hypoglycemia (as pre-specified)

3 Symptomatic and asymptomatic – exploratory analysis - treated set, model without baseline hypoglycemia

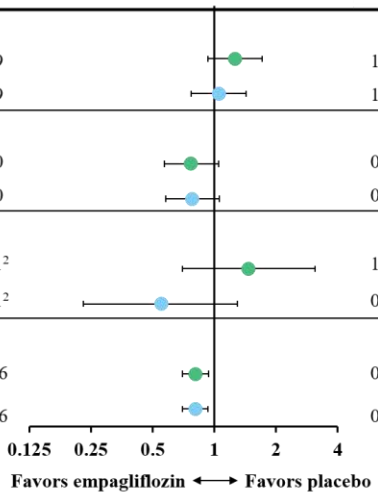
The treated set comprised all patients who were treated with at least 1 dose of randomised study medication

The hypoglycemia results for the higher empagliflozin doses (i.e. 10 and 25 mg) were generally consistent with the findings for empagliflozin 2.5 mg, with reductions in patient-reported events with blood glucose levels below 54 mg/dL (Figure 9).

Overall, empagliflozin treatment did not increase the risk of hypoglycemia in patients with type 1 diabetes.

Figure 9 Hypoglycemia results for empagliflozin 10 and 25 mg

		Empagliflozin		Placebo		Rate Ratio (95% CI)	p-value
		N	Events, n	N	Events, n		
Key secondary[1] hypoglycemia endpoint (week 1-26)	EASE-3 (week 1–26)						
	Empagliflozin 10 mg	244	1423	238	1339	1.26 (0.93, 1.71)	0.1438
	Empagliflozin 25 mg	242	1216	238	1339	1.05 (0.77, 1.43)	0.7543
	EASE-2 (week 1–26)						
	Empagliflozin 10 mg	243	1327	239	1870	0.77 (0.57, 1.05)	0.0972
	Empagliflozin 25 mg	241	1333	239	1870	0.78 (0.58, 1.06)	0.1180
Severe hypoglycemia (week 1-26)	EASE-2 and EASE-3 pooled (week 1–52/1–26)						
	Empagliflozin 10 mg	491	20/33[2]	484	15/21[2]	1.47 (0.70, 3.10)	0.3095
	Empagliflozin 25 mg	489	13/14[2]	484	15/21[2]	0.55 (0.23, 1.29)	0.1695
Patient-reported[3] hypos with BG <54 mg/dl	EASE-2 and EASE-3 pooled (week 1–52/1–26)						
	Empagliflozin 10 mg	491	9133	484	11446	0.81 (0.70, 0.94)	0.0043
	Empagliflozin 25 mg	489	9022	484	11446	0.81 (0.70, 0.93)	0.0035



Negative binomial model; BG: blood glucose

1 Rate of investigator-reported symptomatic hypoglycemic AEs with confirmed plasma glucose <54 mg/dL and/or severe hypoglycemic events – confirmatory analysis – FAS (on-treatment), model including baseline hypoglycemia

2 Number of patients/events – exploratory analysis - treated set, model without baseline hypoglycemia

3 Symptomatic and asymptomatic – exploratory analysis - treated set, model without baseline hypoglycemia

The treated set comprised all patients who were treated with at least 1 dose of randomised study medication

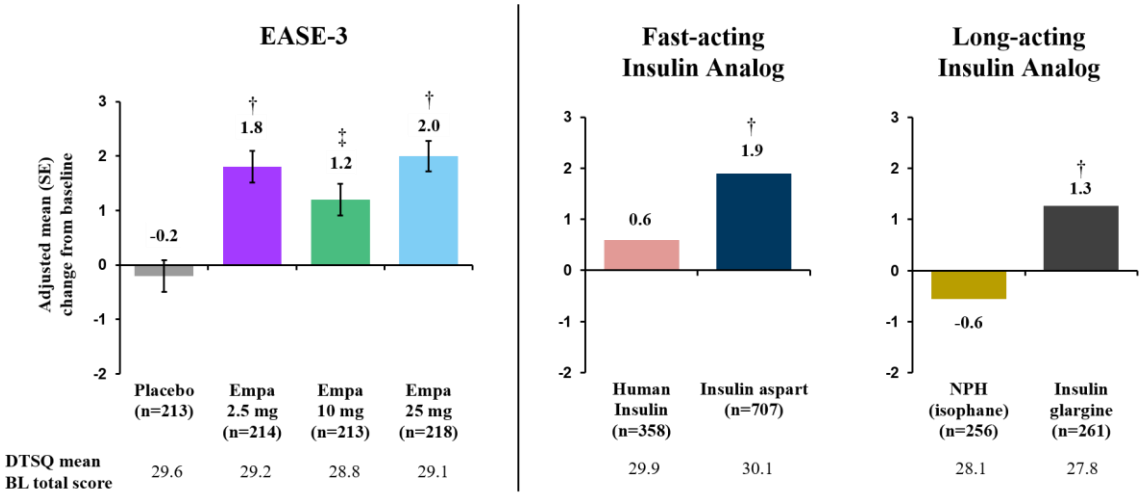
3.4 Improved diabetes treatment satisfaction with empagliflozin 2.5 mg

Patient-centered healthcare is based on informed treatment choices by patients, in line with their individual needs, values, and preferences. In the EASE Phase 3 clinical studies, patient-reported outcome (PRO) measures were used for assessing the patients' perception of their treatment. This analysis was pre-specified, but not included in the confirmatory testing hierarchy.

The Diabetes Treatment Satisfaction Status Questionnaire (DTSQs) total score was used to assess the overall satisfaction of patients with their treatment. In EASE-3, the DTSQ total score was significantly increased with empagliflozin treatment after 26 weeks (Figure 10). The mean change from baseline versus placebo for empagliflozin 2.5 mg was +2.02 points (95% CI 0.90, 3.13). This effect was similar in EASE-2 and sustained over 52 weeks (Section 8.6.4).

To contextualize these results, the near 2-point improvement in the DTSQs total score with empagliflozin 2.5 mg dose on top of intensified insulin therapy is similar to what has been previously observed with the short-acting insulin analog aspart and the long-acting insulin analog glargine versus human insulin and NPH (also known as isophane) insulin, respectively; see Figure 10 and (26, 27).

Figure 10 Change from baseline in DTSQs total score in EASE-3 and observed for insulin analogs



Exploratory analyses; † p<0.001; ‡ p<0.01 for difference versus control

3.5 Efficacy of empagliflozin 10 and 25 mg was sustained over 52 weeks

In the EASE-2 trial, the mean change in HbA_{1c} in the empagliflozin 10 mg and 25 mg treatment groups was approximately -0.5% compared with placebo after 26 weeks (Table 3). Body weight was reduced by about 3 kg with empagliflozin. The time spent in the target glucose range (between 70 to 180 mg/dL) was increased by approximately 13%. This translates to 3 additional hours per day in the glucose target range. The total insulin dose was reduced by about 13%, and systolic and diastolic blood pressure were reduced by about 2 to 3 mmHg. All effects were sustained over 52 weeks.

Table 3 Overview of the efficacy results in the EASE-2 trial

Mean change from baseline versus placebo (95% CI)		26 Weeks		52 Weeks	
		Empa 10 mg	Empa 25 mg	Empa 10 mg	Empa 25 mg
HbA_{1c}, %	FAS analysis	**-0.54**† (-0.65, -0.42)	**-0.53**† (-0.65, -0.42)	**-0.39**§ (-0.52, -0.26)	**-0.45**§ (-0.58, -0.32)
	mITT analysis	**-0.53**† (-0.64, -0.42)	**-0.51**† (-0.62, -0.40)	**-0.37**§ (-0.49,-0.25)	**-0.45**§ (-0.57, -0.32)
Body weight, kg		**-2.69**† (-3.26, -2.11)	**-3.27**† (-3.84, -2.70)	**-3.20**§ (-3.93, -2.46)	**-3.57**§ (-4.29, -2.84)
CGM time in range, %		**11.86**† (9.87, 13.84)	**12.87**† (10.89, 14.85)	**12.17**§ (9.95, 14.39)	**12.52**§ (10.34, 14.70)
Total daily insulin dose, %		**-13.29**† (-15.88, -10.70)	**-12.61**† (-15.19, -10.02)	**-11.99**§ (-15.13, -8.85)	**-12.91**§ (-16.04, -9.78)
SBP, mmHg		**-2.1**§ (-4.1, -0.1)	**-3.7**‡ (-5.7, -1.7)	**-3.4**§ (-5.6, -1.2)	**-4.7**§ (-6.9, -2.5)
DBP, mmHg		**-1.3**§ (-2.7, 0.0)	**-2.3**‡ (-3.6, -1.0)	**-1.7**§ (-3.1, -0.3)	**-1.5**§ (-2.9, -0.2)

Confirmatory analyses for Week 26; † $p<0.0001$; ‡ $p<0.001$; § $p<0.05$ (nominal)

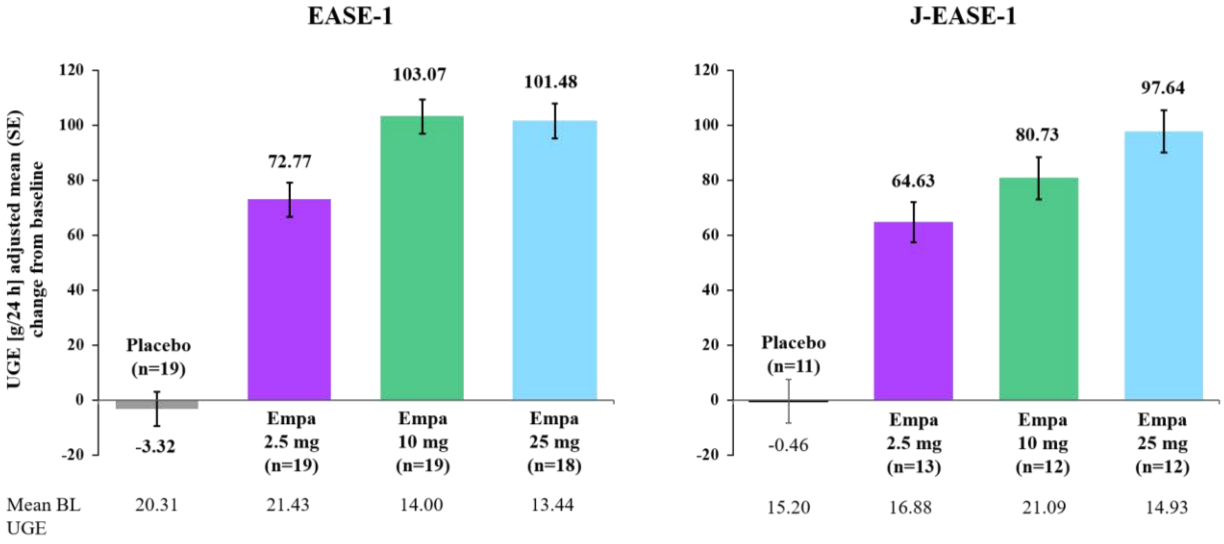
FAS: full analysis set, mITT: modified intention-to-treat set, CGM continuous glucose monitoring, SBP: systolic blood pressure, DBP: diastolic blood pressure

3.6 Consistent gluco-metabolic benefits for empagliflozin 2.5 mg in Phase 2 trials

EASE-1, performed in Europe, and J-EASE-1, performed in Japan, were randomized, double-blind, placebo-controlled dose-finding trials that tested empagliflozin 2.5, 10 and 25 mg over 4 weeks. In EASE-1 all patients were White Europeans, with 71% male patients and 29% female patients (Section 8.5.2.2). In J-EASE all patients were Asian (46% male and 54% female). The mean age was 41 years (EASE-1) and 45 years (J-EASE-1). Mean baseline BMI was 26 kg/m^2 (EASE-1) and 23 kg/m^2 (J-EASE-1). Mean baseline HbA_{1c} was 8.2% (EASE-1) and 8.1% (J-EASE-1).

The primary exploratory endpoint in both trials was the change from baseline in urinary glucose excretion (UGE) after 7 days of treatment. UGE is the main pharmacodynamic parameter of SGLT2 inhibitors. Both trials showed a substantial UGE increase versus placebo in all empagliflozin dose groups (Figure 11). Empagliflozin 2.5 mg provided 70% of the effect of the higher doses in EASE-1. This suggests a meaningful pharmacodynamic effect of the lower dose that translates into meaningful efficacy results.

Figure 11 Change from baseline in urinary glucose excretion after 7 days of treatment in the Phase 2 trials



UGE: urinary glucose excretion

All empagliflozin doses in the Phase 2 trials showed improved glycemic control and weight loss. There was an increase in the time in glucose target range and no increase in hypoglycemic events. No DKA events were reported. Table 4 provides an overview of the main efficacy and safety results.

Table 4 Overview of Phase 2 results

	EASE-1			J-EASE-1		
	Empa 2.5 mg n=19	**Empa 10 mg n=19**	**Empa 25 mg n=18**	**Empa 2.5 mg n=13**	**Empa 10 mg n=12**	**Empa 25 mg n=12**
Efficacy: Mean difference versus placebo (95% CI)						
HbA_{1c} at Day 28, %	**-0.35**§ (-0.62, - 0.09)	**-0.36**§ (-0.62, - 0.10)	**-0.49**§ (-0.75, - 0.22)	**-0.20** (-0.48, 0.08)	**-0.35**§ (-0.63, - 0.07)	**-0.20** (-0.49, 0.08)
Weight at Day 28, kg	**-1.53**† (-2.40, -0.66)	**-1.78**† (-2.65, -0.90)	**-1.85**† (-2.73, -0.97)	**-1.37**§ (-2.29, -0.44)	**-1.47**§ (-2.42, -0.52)	**-1.70**† (-2.64, - 0.75)
Time in glucose range[1], Week 4, hours/day	**+1.28** (-0.25, 2.80)	**+1.52** (-0.02, 3.05)	**+2.99**§ (1.45, 4.53)	**+4.01**† (1.75, 6.27)	**+2.66**§ (0.38, 4.93)	**+4.02**† (1.77, 6.26)
Safety						
General safety	Comparable to type 2 diabetes			Comparable to type 2 diabetes		
DKA	No reported cases			No reported cases		
Severe hypoglycemia	One case on placebo			No reported cases		
Genital infections	No reported cases			Two cases on empagliflozin		

† $p<0.001$; § $p<0.05$

1 Time in range defined as >70 to 180 mg/dL

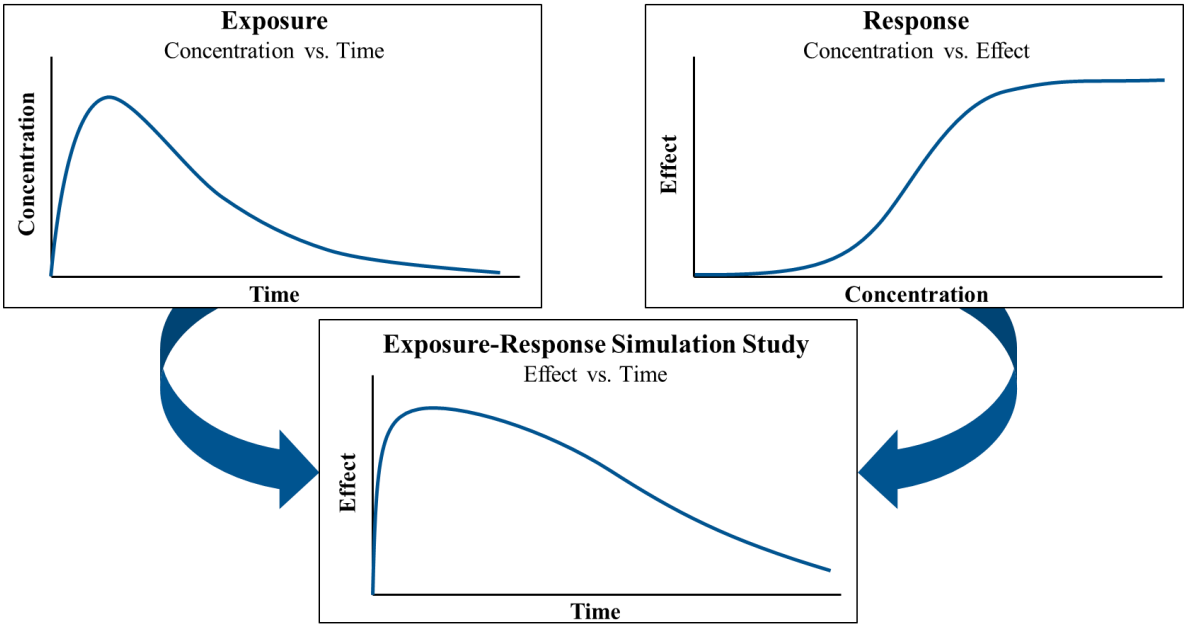
3.7 Consistent HbA_{1c} reduction with empagliflozin 2.5 mg in exposure-response simulation studies

Since the empagliflozin 2.5 mg dose was evaluated in only one of the Phase 3 trials (EASE-3), the effect of this dose was simulated in the other Phase 3 trial (EASE-2) based on exposure-response analyses.

The FDA recognizes that data from alternative sources (from Phase 2 trials and/or exposure-response modeling) can provide substantial evidence (28).

The general concept of an exposure-response analysis is shown in Figure 12. The analysis combines an exposure (or pharmacokinetic) model component that describes the time course of a drug in plasma and a response (or pharmacodynamic) model component (in our case HbA_{1c}) that relates the plasma concentration to the drug effect in order to describe the time course of the effect intensity resulting from the administration of a certain dosage regimen.

Figure 12 General concept of an exposure-response analysis

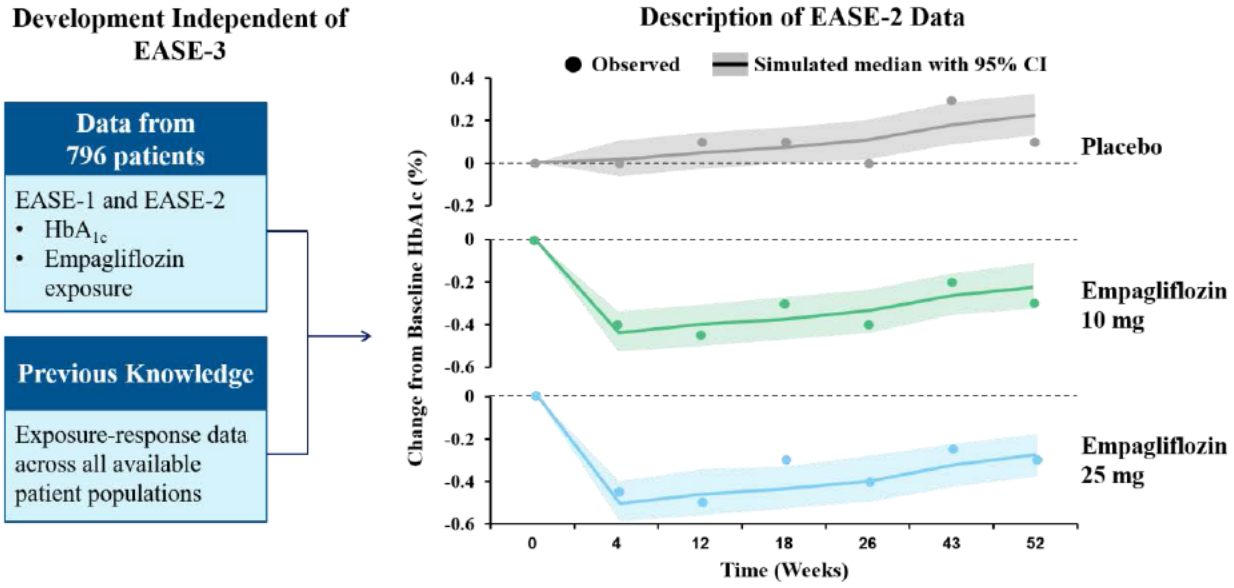


Adapted from (29)
In the 'Response' plot, concentration is displayed on a log scale

Exposure-response model development

In the first step, the model for empagliflozin 2.5 mg in patients with type 1 diabetes was developed using data only from the Phase 2 trial EASE-1 and the Phase 3 trial EASE-2. This ensured independence of the simulation from EASE-3. In addition, previous knowledge from exposure-response analyses conducted across all available patient populations was used. The developed model was able to describe the time course of HbA_{1c} lowering in all dose groups in the EASE-2 population up to 52 weeks of treatment (Figure 13).

Figure 13 Exposure-response model development



Exposure-response model validation

As a second step, the model was validated by simulating the outcome of the EASE-3 trial itself. Simulating the outcome of a study that is not included in the exposure-response analysis is considered the gold standard for model validation. Indeed, the simulations were able to replicate the actual results of the trial for HbA_{1c} for all empagliflozin dose groups (Table 5). It was therefore concluded that the model was suitable to investigate untested scenarios.

Table 5 Model validation: observed and simulated HbA_{1c} reduction after Week 26 in EASE-3

	Observed in EASE-3	**Simulated for validation**
Empagliflozin dose group	Mean (SE)	Mean (SE)
2.5 mg	-0.28 (0.07)	-0.29 (0.05)
10 mg	-0.45 (0.07)	-0.47 (0.05)
25 mg	-0.52 (0.07)	-0.53 (0.04)

Exposure-response simulation study

As a final step, the validated model was used to perform clinical trial simulations to evaluate the effect of the empagliflozin 2.5 mg dose in the EASE-2 population. For this purpose, 500 trials were simulated, each with the same number of patients included in the EASE-2 study per dose group (239).

The outcome of the simulations were consistent with the results for empagliflozin 2.5 mg in the EASE-3 trial. Simulations showed a mean HbA_{1c} reduction versus placebo in the EASE-2 population with empagliflozin 2.5 mg of -0.29 (95% CI -0.38, -0.20) after 26 weeks and -0.29 (95% CI -0.38, -0.20) after 52 weeks.

A second exposure-response analysis also yielded results consistent with the observed effect. This model described the relation between empagliflozin exposure, changes in total daily insulin dose and mean daily glucose and their joint effect on HbA_{1c}. Clinical trial simulations using this model were consistent with the HbA_{1c} reductions observed in the EASE trials and the simulations based on the model described above. The mean placebo-corrected HbA_{1c} reduction was -0.32 (95% CI -0.53, -0.11), both after 26 weeks and 52 weeks.

These results provide additional evidence of empagliflozin 2.5 mg efficacy independent of EASE-3.

3.8 Summary of efficacy

Treatment with empagliflozin 2.5 mg provided an HbA_{1c} reduction versus placebo comparable to currently approved therapy as adjunct to insulin in type 1 diabetes in the U.S. (pramlintide). This was consistently observed across the clinical trials and the exposure-response simulation study (Table 6).

Table 6 Overview of HbA_{1c} results for empagliflozin 2.5 mg across studies

	Phase 3	**Phase 2**		**Exposure-Response Simulation Study**	
	EASE-3	**EASE-1**	**J-EASE-1**	**EASE-2 Simulation**	
	26 weeks	**4 weeks**	**4 weeks**	**26 weeks**	**52 weeks**
Mean change in HbA_{1c} versus placebo (95% CI) [%]	-0.28 (-0.42, -0.15)	-0.35 (-0.62, -0.09)	-0.20 (-0.48, 0.08)	-0.29 (-0.38, -0.20)	-0.29 (-0.38, -0.20)

Empagliflozin 2.5 mg provided improvements for additional outcomes in EASE-3:

- Reduction in body weight versus placebo: -1.8 kg (95% CI -2.3, -1.2), p<0.0001
- Reduction in systolic blood pressure versus placebo: -2.1 mmHg (95% CI -3.9, -0.2), p=0.0270
- Improved diabetes treatment satisfaction versus placebo, as measured by DTSQs: +2.02 points (95% CI 0.90, 3.13), p<0.0001
- No increase in hypoglycemia

The HbA_{1c} reduction with empagliflozin 2.5 mg was modest but meaningful since any decrease in HbA_{1c} without substantial hypoglycemia or weight gain is desirable in patients type 1 diabetes. Importantly, these gluco-metabolic improvements observed with empagliflozin 2.5 mg treatment are similar to those observed for pramlintide, the only currently approved adjunct to insulin therapy in the U.S.

4. Treatment with empagliflozin 2.5 mg was well tolerated

Overall, the treatment with empagliflozin 2.5 mg was well tolerated, and the safety profile was generally comparable to the safety profile of empagliflozin in patients with type 2 diabetes.

The observed incidence of DKA for empagliflozin 2.5 mg was lower than that of the higher doses and was similar to that observed in the placebo group.

These observations are in the context of a randomized controlled clinical trial wherein

- Investigators and patients were trained on the risk of DKA, including the atypical presentation and caution around insulin dose reduction.
- Patients received a point-of-care device to measure ketones and an electronic diary for daily recording of ketone measurements and symptoms suggestive of DKA.
- During run-in and the first 4 weeks of treatment, patients were advised to test fasting ketone levels daily to provide baseline information, thereafter two–three times per week or in case of any symptoms, regardless of glucose levels. Patients were advised to seek medical care in case of ketone levels above 1.5 mmol/L.
- In case of a suspected DKA, the investigator and treating physician was instructed to direct appropriate additional tests.

Additionally, during the study, a trial information card was implemented. Patients were to carry this card at all times and to present the card to any treating physician or healthcare professional who may not be familiar with trial procedures and may not recognize that SGLT2 inhibitors can modify the presentation of DKA (e.g., lower than anticipated blood glucose values). For more details, see Section 8.7.2.4.

In total, in the Phase 3 program, 1221 patients were exposed to empagliflozin. This resulted in 809 patient-years of exposure with empagliflozin (117 patient-years with empagliflozin 2.5 mg).

Data from the higher empagliflozin doses can help to establish an upper boundary for general safety with the 2.5 mg dose. In the safety analyses, data for empagliflozin 10 and 25 mg doses were pooled across the two Phase 3 trials.

The main safety analyses were based on the treated set, which comprised all patients who were treated with at least 1 dose of randomised study medication.

4.1 General safety

Adverse events occurred with similar frequency among the groups (Table 7).

An increase in drug-related events and adverse events leading to discontinuation with all empagliflozin doses could be explained by known effects of SGLT2 inhibitors including genitourinary tract infections and ketosis-related events (see Section 8.7.2.2).

Table 7 Overview of adverse events in EASE-3 and the pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo N (%)	Empa 2.5 mg N (%)	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Patients with any AE	**203 (84.2)**	**194 (80.5)**	433 (89.5)	441 (89.8)	428 (87.5)
Drug-related AEs	**56 (23.2)**	**70 (29.0)**	158 (32.6)	221 (45.0)	226 (46.2)
AEs leading to treatment discontinuation	**2 (0.8)**	**8 (3.3)**	14 (2.9)	29 (5.9)	18 (3.7)
Serious AEs	**16 (6.6)**	**13 (5.4)**	44 (9.1)	64 (13.0)	42 (8.6)
Fatal AEs	**0**	**0**	0	0	1 (0.2)

Treated set, on-treatment analysis

Adverse events of special interest were analyzed based on the mechanism of action of SGLT2 inhibitors and known safety findings within the drug class (Table 8).

Severe hypoglycemia occurred with similar frequency between treatment groups. Expectedly, an increase in genital infections was observed in the empagliflozin groups, though the relative increase compared with placebo was lower with the empagliflozin 2.5 mg dose. The proportion of patients experiencing DKA was similar between the 2.5 mg dose and placebo, while an increase was observed for the higher doses of 10 mg and 25 mg. A detailed analysis of DKA is provided in the subsection 4.2.

Table 8 Adverse events of special interest in EASE-3 and the pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo N (%)	Empa 2.5 mg N (%)	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Severe hypoglycemia					
Investigator-reported	**8 (3.3)**	**6 (2.5)**	22 (4.5)	21 (4.3)	17 (3.5)
Adjudicated	**6 (2.5)**	**3 (1.2)**	15 (3.1)	20 (4.1)	13 (2.7)
Genital infections	**6 (2.5)**	**10 (4.1)**	16 (3.3)	55 (11.2)	56 (11.5)
Volume depletion	**3 (1.2)**	**1 (0.4)**	8 (1.7)	12 (2.4)	16 (3.3)
Urinary tract infections	**13 (5.4)**	**13 (5.4)**	45 (9.3)	49 (10.0)	39 (8.0)
Acute renal impairment	**0**	**0**	3 (0.6)	1 (0.2)	4 (0.8)
Hepatic events	**1 (0.4)**	**1 (0.4)**	7 (1.4)	8 (1.6)	8 (1.6)
Lower limb amputations	**0**	**1 (0.4)**	0	0	0
Bone fractures	**2 (0.8)**	**5 (2.1)**	8 (1.7)	14 (2.9)	5 (1.0)
Malignancy	**2 (0.8)**	**2 (0.8)**	3 (0.6)	0	0
Cardiovascular and neurological events (adjudicated)	**0**	**2 (0.8)**	1 (0.2)	1 (0.2)	2 (0.4)
DKA (adjudicated as certain)	**3 (1.2)**	**2 (0.8)**	6 (1.2)	21 (4.3)	16 (3.3)

Treated set, on-treatment analysis

4.2 DKA and ketosis

All potential events of DKA were adjudicated in a blinded fashion by an independent, external Clinical Endpoint Committee (CEC) in line with FDA recommendations.

Investigator-reported adverse events indicative of DKA as well as elevated patient-measured beta-hydroxybutyrate (BHB) values were sent for adjudication. DKA adjudication was based on adverse event reporting and laboratory assessment (see Section 8.2.1 for details).

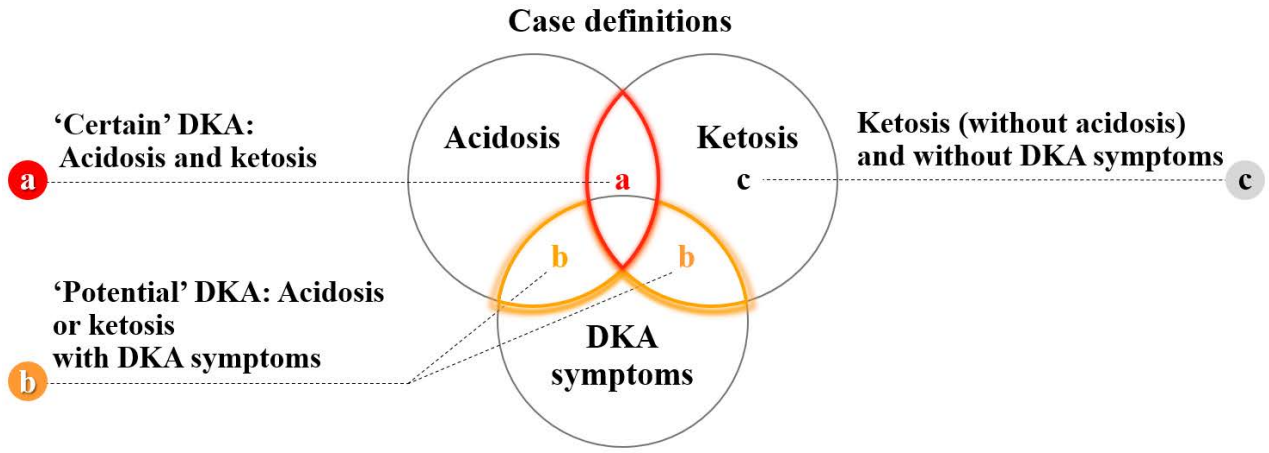
The CEC adjudicated cases according to the charter definitions, which were pre-defined based on international guidelines (ADA, European Association for the Study of Diabetes/EASD) and the adjudication charter agreed by the FDA:

- 'Certain' ketoacidosis: if both acidosis and ketosis was present
- 'Potential' ketoacidosis: if either acidosis or ketosis was present together with symptoms suggestive of DKA
- 'Ketosis': elevated ketones without acidosis and without DKA symptoms
- 'Unlikely': absence of ketosis and acidosis

An illustration of these categories is provided in Figure 14. All events in the DKA adjudication were classifiable.

In addition to the level of certainty, all episodes were classified according to severity based on pH/bicarbonate values or the degree of neurological symptoms.

Figure 14 Parameters for DKA adjudication



Adjudicated events of DKA with empagliflozin 2.5 mg

In EASE-3 the frequency and yearly event rate of DKA events adjudicated by the CEC as 'certain' in the empagliflozin 2.5 mg treatment group was low and similar to the placebo group (Table 9 and Figure 15 below).

For a broader assessment of DKA, a combined analysis of 'certain' cases and 'potential' cases was performed. The observed event rate for this a combined analysis of 'certain' cases and 'potential' cases was also similar between empagliflozin 2.5 mg and placebo (Table 9 and Figure 15).

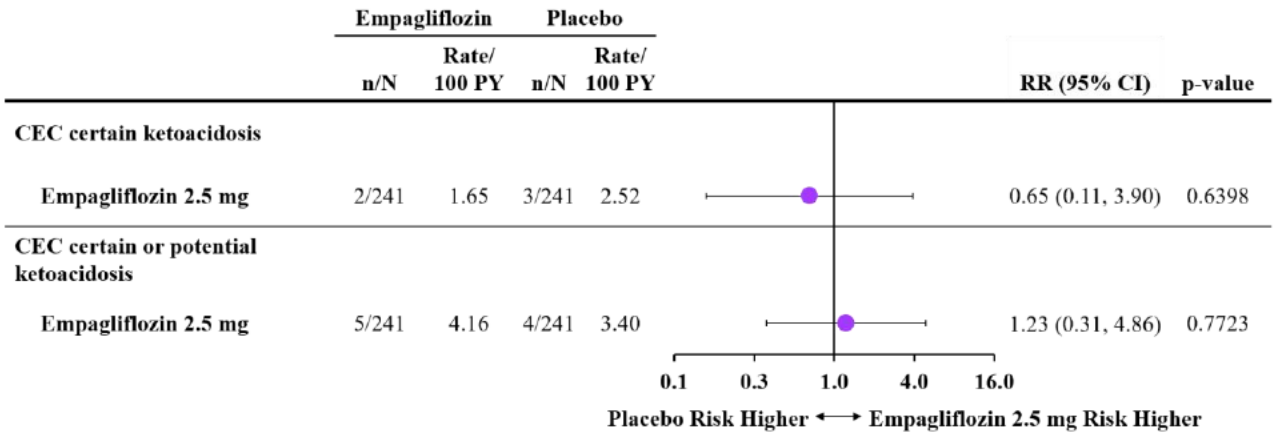
Both episodes of 'certain DKA' in the empagliflozin 2.5 mg group were categorized as mild. None of the 'potential DKA' episodes in the 2.5 mg dose group required hospitalization. Discontinuation of trial medication due to DKA was infrequent for empagliflozin 2.5 mg (1 patient/0.4%); see Section 8.7.2.2.

Table 9 Adjudicated DKA with empagliflozin 2.5 mg in EASE-3

	Placebo	Empa 2.5 mg
Patients, N (100%)	241	241
Patients with certain DKA, N (%)	3 (1.2)	2 (0.8)
Number of events (rate per 100 patient years)	3 (2.52)	2 (1.65)
Events by severity		
Severe	1	0
Moderate	1	0
Mild	1	2
Patients with certain or potential DKA, N (%)	4 (1.7)	4 (1.7)
Number of events (rate per 100 patient years)	4 (3.36)	5 (4.12)
DKA events with blood glucose <250 mg/dL	0	2
Events by severity		
Severe	1	0
Moderate	1	0
Mild	2	5

Treated set, on-treatment analysis

Figure 15 Adjudicated DKA events with empagliflozin 2.5 mg in EASE-3



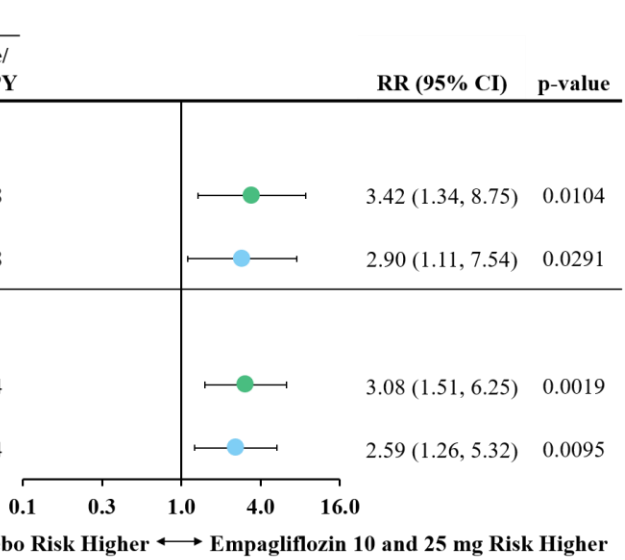
Adjusted event rates, negative binomial model

Adjudicated events of DKA with empagliflozin 10 mg and 25 mg

The proportion of patients experiencing DKA as well as the event rate was higher with the empagliflozin 10 and 25 mg doses as compared with placebo (see Figure 16 and Table 10 and below, and Section 8.7.2.4).

Figure 16 Adjudicated DKA events with empagliflozin 10 and 25 mg in the Phase 3 trials

	Empagliflozin		Placebo			
	n/N	Rate/ 100 PY	n/N	Rate/ 100 PY	RR (95% CI)	p-value
CEC certain ketoacidosis						
Empagliflozin 10 mg	21/491	6.10	6/484	1.78	3.42 (1.34, 8.75)	0.0104
Empagliflozin 25 mg	18/489	5.17	6/484	1.78	2.90 (1.11, 7.54)	0.0291
CEC certain or potential ketoacidosis						
Empagliflozin 10 mg	37/491	11.20	12/484	3.64	3.08 (1.51, 6.25)	0.0019
Empagliflozin 25 mg	32/489	9.43	12/484	3.64	2.59 (1.26, 5.32)	0.0095



Adjusted event rates, negative binomial model

More than one third of the episodes of 'certain' ketoacidosis in empagliflozin 10 and 25 mg groups were atypical, with blood glucose values were <250 mg/dL. All episodes of certain DKA occurred in the presence of a precipitating factor (Table 10). The most common ones were acute illness, infection and reduced insulin intake such as insulin delivery malfunction. One percent of patients in the higher dose groups discontinued the trial medication due to DKA (see Section 8.7.2.4).

Table 10 Precipitating factors for adjudicated certain DKA in the Phase 3 trials

	Pooled Phase 3 trials (up to 52 weeks)		
	Placebo	Empa 10 mg	Empa 25 mg
Number of patients, N (100%)	484	491	489
Patients with 'certain' DKA, N (%)	6 (1.2)	21 (4.3)	16 (3.3)
'Certain' DKA events (rate per 100 patient-years)	6 (1.77)	21 (5.94)	18 (5.05)
'Certain' events with BG <250 mg/dL	0	9	5
Precipitating factors, number of episodes			
Concomitant illness/infection	2	7	12
Inadequate insulin administration[1]	1	11	10
Dietary changes/carbohydrate depletion	1	4	1
Severe dehydration	1	1	4
Other	3	9	4
None	0	0	0

Treated set, on-treatment analysis. BG: blood glucose
1 Including insulin delivery malfunction

Subgroup analyses of DKA with empagliflozin 10 mg and 25 mg

Due to the low number of events, subgroup analyses were not feasible for the 2.5 mg dose. Subgroup analyses by baseline characteristics were therefore performed for the empagliflozin 10 and 25 mg doses to identify baseline characteristics that could potentially be associated with a higher risk of DKA.

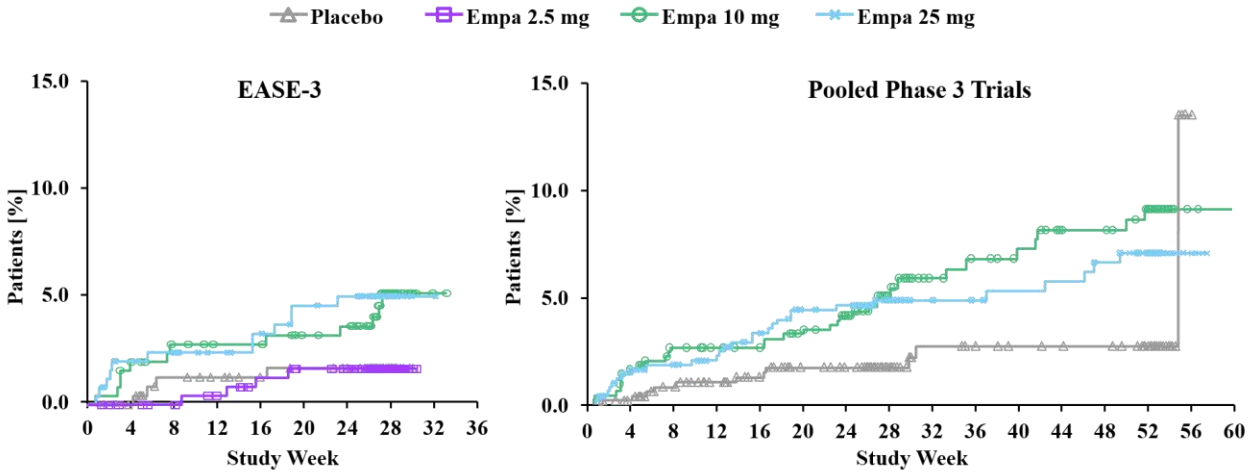
Baseline characteristics identified to be associated with a higher rate of 'certain or potential' DKA in all treatment groups, including placebo, were insulin pump use and previous history of DKA.

A consistently elevated DKA risk with empagliflozin 10 and 25 mg as compared with placebo was found across all subgroups, with the highest relative to placebo increase in female patients (Section 8.7.2.4).

No time dependency for DKA events

To address whether patients were more likely to develop DKA at specific times during the trials, the time to the patients' first certain or potential DKA event was analyzed. This analysis showed an equal distribution of DKAs over time, both in the 26-week trial EASE-3 and the 52-week trial EASE-2 (Figure 17).

Figure 17 Time to first adjudicated certain or potential DKA event in EASE-3 and the pooled Phase 3 trials



Ketone-related events

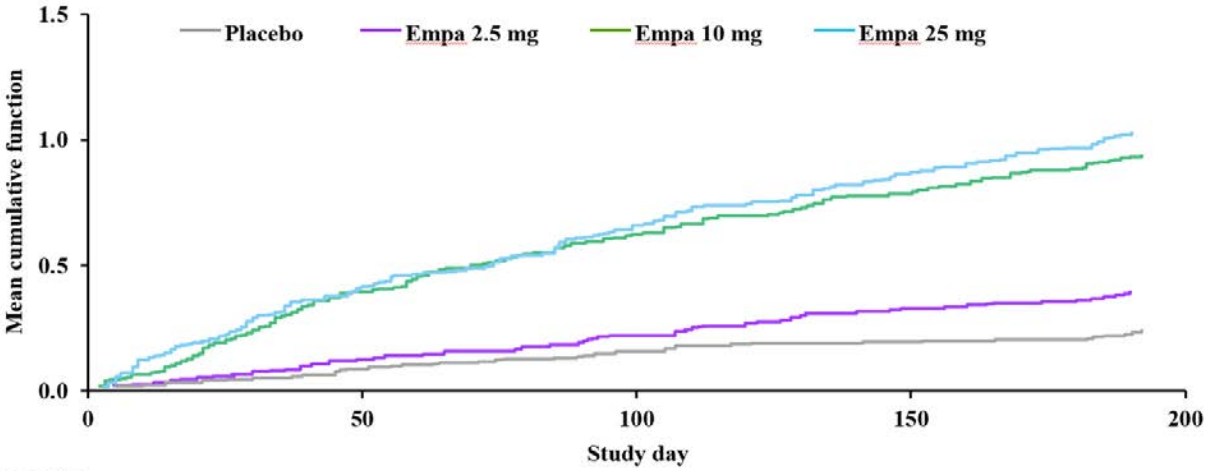
Because DKA is always preceded by ketosis, an analysis of all ketone-related events was performed. This analysis included all events of:

1. Adjudicated certain or potential DKA
2. Adjudicated ketosis
3. Ketone values >1.5 mmol/L, even if not qualifying as triggers for adjudication

The average number of ketone-related events per patient, accumulated over time, was calculated. An increase in ketone-related events versus placebo was seen with all empagliflozin doses (Figure 18), but a clear separation between the curves for empagliflozin 2.5 mg and the higher doses was observed.

In summary, based on the analysis of all ketone-related events, the risk of DKA is anticipated to be lower with empagliflozin 2.5 mg than with the 10 and 25 mg doses.

Figure 18 Average number of ketone-related events per patient, accumulated over time in EASE-3



Patients at risk					
Placebo	241	232	225	221	5
Empa 2.5 mg	241	236	233	227	13
Empa 10 mg	248	240	233	227	13
Empa 25 mg	245	237	228	223	9

4.3 Proposed risk mitigation measures in the post-marketing setting

The data from the EASE Phase 3 program suggest a lower risk for DKA with empagliflozin 2.5 mg dose than the higher doses. Measures similar to those employed in the clinical trial are proposed for implementation in the post-marketing setting for empagliflozin 2.5 mg.

Dose selection is an integral part of DKA risk mitigation

The EASE-3 trial showed no imbalance in the frequency of DKA between empagliflozin 2.5 mg and placebo, in the context of a controlled clinical trial setting. This indicates that the low dose selection itself is an important factor for DKA risk mitigation in patients with type 1 diabetes.

However, given the inherent nature of the disease and the mechanism of action of SGLT2 inhibition, a risk of DKA in real-world use cannot be excluded. Specific measures will therefore be implemented to minimize the risk of DKA in the real world setting.

The proposed separate brand from the empagliflozin type 2 diabetes brand will be a key element. Having a type 1 diabetes-specific brand gives the opportunity to provide product information and educational materials specifically tailored to patients with type 1 diabetes and their caregivers. Such material will focus on specific DKA risk mitigation measures in patients with type 1 diabetes such as ketone monitoring.

A dedicated brand will also help to reduce the risk of potential medication errors.

The proposed risk mitigation measures are based on the mechanism of action of empagliflozin, data from the EASE clinical trials as well as the scientific literature (Table 11). These measures will target prescribers, pharmacists, emergency care providers and patients.

A post-marketing safety study is planned to further assess the safety of empagliflozin 2.5 mg, including the risk of DKA, in patients with type 1 diabetes in routine clinical practice setting.

Table 11 Risk mitigation measures

Target Group: Prescribers and Pharmacists	
Proposed measures	**Key recommendation**
Prescribing Information	Cautious insulin dose reductions, especially in patients with lower insulin needs
	Cautious use in patients with risk factors (female sex, insulin pump use, very low carbohydrate diet and eating disorders, acute illness, alcohol abuse or bingeing, severe dehydration, history of DKA, lower insulin dose requirements)
Patient Counselling Information	Temporary discontinuation in clinical situations known to predispose to DKA (e.g. prolonged fasting, acute illness, surgery and insulin pump malfunction)
	Instructions to patients on: • Frequent ketone monitoring (preferably blood ketones) during the first few weeks of treatment, thereafter - in case of symptoms even if blood glucose is not elevated and in situations where clinically indicated • Steps to take when ketones are elevated and when to seek medical care • The need to carry the Wallet Card at all times • The need to inform their doctor in case of prolonged fasting, acute illness, surgery or insulin pump malfunction

Table 11 (cont'd) Risk mitigation measures

Target group: Patients	
Proposed measures	**Key recommendation**
Medication Guide Wallet Card (hardcopy and digital format)	Carry Wallet Card at all times
	Take insulin as instructed
	Follow sick-day plan, in case of sudden illness or sudden infection
	Check ketones (preferably blood ketones) in any of the situations known to pre-dispose to DKA
	Ensure adequate hydration
	Avoid low carbohydrate diets and excessive alcohol intake
	Inform doctor about sudden illness, planned surgery, insulin pump issues
	In case of blood ketones of >1.5 mmol/L, which do not improve after hydration, insulin dose increase, carbohydrate intake, seek medical care immediately
Target Group: Emergency Care Providers	
Proposed measures	**Key recommendation**
Wallet Card	Measure blood ketones in case of symptoms indicative of DKA, even if blood glucose levels are below those typically expected for DKA (often less than 250 mg/dL)
	If DKA is suspected – discontinue empagliflozin, evaluate and treat promptly
Prescribing Information	See above

4.4 Summary of safety

- Empagliflozin did not increase the risk of severe hypoglycemia
- No imbalance in the frequency of DKA was observed between empagliflozin 2.5 mg and placebo, in the context of the clinical trial. Low-dose selection appears to be an important factor for DKA risk mitigation for SGLT2 inhibitor use in this population.
- Physician and patient education will be integral to minimize the risk of DKA in the real world setting.

5. Preference for a low-dose SGLT inhibitor was observed in a patient survey

While overall patient treatment satisfaction was shown to increase with empagliflozin treatment as demonstrated by the DTSQ results in the EASE program, the overall patient perspective with respect to the key benefit and risk attributes of therapy was evaluated using a survey.

This patient survey (30) conducted in 701 patients from the U.S., Canada and Germany, assessed the preferences and the value patients with type 1 diabetes place on various efficacy and safety outcomes (as observed in clinical trials) for the following adjunct to insulin treatment options:

- A drug profile of a low-dose SGLT inhibitor (for example comparable to empagliflozin 2.5 mg)
- A high-dose SGLT inhibitor, a drug profile providing more efficacy at the expense of a higher DKA risk (for example comparable to sotagliflozin 400 mg)
- A drug profile comparable to pramlintide, the only approved adjunct-to-insulin therapy in type 1 diabetes in the U.S.

The results of the survey were based on conjoint analysis, a methodology commonly used to measure patient preference data. The survey revealed that a drug profile comparable to a low-dose SGLT inhibitor appears to be the preferred therapy option for the majority patients (83% of preference shares) as compared with a high-dose SGLT inhibitor option (8%) or a drug profile comparable to pramlintide (9%) The results for the overall preference outcomes were consistent in the U.S. respondent subgroup where 95% of the preference outcome was also for a low-dose SGLT inhibitor option.

6. Extent of evidence for empagliflozin 2.5 mg effects

The EASE clinical program comprised of multiple RCTs including two Phase 3 trials, provides the evidence for the overall assessment of efficacy of empagliflozin in type 1 diabetes.

This body of evidence, including the upper bound of safety as established by the evaluation of higher doses (10 and 25 mg), provides the basis to assess the safety for empagliflozin 2.5 mg. Within the EASE program, a lower risk of DKA was observed for the empagliflozin 2.5mg dose relative to higher doses.

The EASE-3 trial, which studied empagliflozin 2.5 mg, satisfies several criteria for establishing clinical evidence of effectiveness (31) as outlined below:

1. **Sound trial design and robust conduct**: EASE-3 was a large international multicentre trial following a real-world care design with a high patient retention rate, 100% source data verification and comprehensive safety signal assessments for DKA and severe hypoglycemia in line with FDA recommendations

2. **Multiple endpoints and meaningful effects:** HbA_{1c} efficacy and effectiveness analyses (near -0.3% effect) plus assessment of other clinically meaningful gluco-metabolic endpoints such as weight (-1.8 kg), hypoglycemia (no observed increase), CGM time in range (+ 1 hour/day) and blood pressure (-2.1 mmHg)
3. **Persuasive statistical evidence**: Highly significant primary analysis ($p<0.0001$) with consistent results in sensitivity analyses (including off-treatment values and alternative methods to handle missing data). Consistent dose response relationship in subgroup analyses and in key secondary endpoints (nominal $p<0.05$ to <0.0001)
4. **Findings in similar population**: EASE-3 efficacy findings were comparable to those in two other independent Phase 2 trials; observations were also consistent in patient populations such as in Japanese patients studied in J-EASE-1
5. **Effect in related disease**: PK/PD/safety/efficacy of empagliflozin fully characterized in type 2 diabetes with clinical effects consistent between type 1 and type 2 diabetes for gluco-metabolic endpoints such as HbA_{1c}, body weight, glucose time in range, and blood pressure
6. **Pharmacologic evidence on clinical effects**: Empagliflozin 2.5 mg's pharmacological effect in terms of UGE of near 70 g/day in type 1 diabetes is a mechanistic basis of consistent clinical effects observed in multiple type 1 diabetes clinical trials and comparable to effects of 10 and 25 mg in type 2 diabetes where clinically-relevant efficacy has been established previously.

Data for empagliflozin 2.5 mg from the EASE-3 trial were consistent with two other randomized controlled trials – EASE-1 and J-EASE-1. Since the empagliflozin 2.5 mg dose was studied in only one of the Phase 3 trials, the effect of this dose was simulated in the Phase 3 trial EASE-2 based on exposure-response analyses. These studies also demonstrated consistency with the data from the three clinical trials (see Section 3.8, Table 6).

The totality of data led to the conclusion that empagliflozin 2.5 mg has the potential to be a treatment option for appropriate patients living with type 1 diabetes.

7. Benefit-Risk Summary

The initial aim of Boehringer Ingelheim was to register empagliflozin at the same doses for type 1 diabetes that were already approved for type 2 diabetes (10 and 25 mg). Since then, data have emerged that suggest a risk of DKA with SGLT2 inhibitor use, in particular in type 1 diabetes using doses available for the treatment of type 2 diabetes (17). Based on this knowledge and the outcome of the EASE clinical development program, Boehringer Ingelheim proposes empagliflozin 2.5 mg as a specific dose for the treatment of adults with type 1 diabetes as an adjunct to insulin therapy.

This lower dose (empagliflozin 2.5 mg) was investigated following the FDA's recommendation. The FDA noted *"safety concerns specific to patients with type 1 diabetes that may warrant exploration of a lower dose"*. The agency also highlighted that *"We expect that the risk/benefit in this population will be different than in the type 2 diabetes population and are uncertain that doses approved for type 2 diabetes are optimal for type 1 diabetes."*

Within the context of these Phase 3 trials, all three empagliflozin doses showed a positive benefit-risk profile. However, the 2.5 mg dose emerged with the most favorable profile given that the risk of DKA in type 1 diabetes was lower than that observed for the 10 and 25 mg doses.

Empagliflozin 2.5 mg yielded:

- HbA_{1c} reductions in the range of 0.3%, comparable to the only approved adjunct therapy in type 1 diabetes in the U.S. (pramlintide)
- Reductions in body weight (-1.8 kg) and systolic blood pressure (-2.1 mmHg)
- No increased risk of hypoglycemia
- Improved diabetes treatment satisfaction as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ)

These Phase 3 results for empagliflozin 2.5 mg are consistent with two randomized controlled Phase 2 trials. Since the 2.5 mg dose was studied in only one of the Phase 3 trials, the effect of this dose was simulated in the other Phase 3 trial based on exposure-response analyses. These studies also demonstrated consistency with the data from the three clinical trials.

While treatment with empagliflozin 2.5 mg was not associated with an increase in the observed rate of DKA as compared with placebo in clinical trial settings, a potential increased risk in the real-world setting cannot be ruled out. Boehringer Ingelheim therefore proposes a package of measures in the post-marketing setting, based on the measures employed in the clinical trial program. Dose-selection is an important element in mitigating the risk of DKA in this context.

The totality of data has led us to the conclusion that empagliflozin 2.5 mg has the potential to be a treatment option for appropriate patients living with type 1 diabetes. Treatment with empagliflozin 2.5 mg can potentially address the unmet need of these patients to improve glycemic control without weight gain and without an increase in severe hypoglycemia.

Therefore, Boehringer Ingelheim proposes to register empagliflozin 2.5 mg as a specific dose for the treatment of adults with type 1 diabetes as an adjunct to insulin therapy.

This type 1 diabetes-specific dose of empagliflozin 2.5 mg is proposed be marketed under a type 1 diabetes standalone brand which is distinct from the brand for empagliflozin currently approved for type 2 diabetes. This will enable healthcare providers and patients to be provided with type 1 diabetes-specific prescribing information and focused education.

Having a type 1 diabetes-specific brand will also enable a post-marketing study to assess the safety of empagliflozin 2.5 mg in patients with type 1 diabetes in routine clinical practice setting.

8. Appendix

This section provides further details of the design and results of the clinical development program of empagliflozin in type 1 diabetes.

8.1 Drug profile

Empagliflozin, a highly selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, decreases the renal reabsorption of glucose, thereby promoting glucose excretion in the urine with a resulting reduction in blood glucose levels. The safety and efficacy profile of empagliflozin has been previously established in a large type 2 diabetes clinical program including the safety and efficacy evaluation of this agent in the EMPA-REG OUTCOME trial in patients with type 2 diabetes and established cardiovascular disease.

8.2 Clinical development program

The clinical development of empagliflozin as an adjunct to insulin in patients with type 1 diabetes started in 2011. Proof of clinical concept in type 1 diabetes adult patients was established in the Phase 2 trials EASE-1, and J-EASE-1. Subsequently, BI initiated the empagliflozin type 1 diabetes Phase 3 trials EASE-3 and EASE-2 in 2015.

8.2.1 Phase 3 trial design

The Phase 3 trial designs were discussed and agreed upon with the FDA. In the EASE-3 and EASE-2 trials, the treatment period was preceded by a 6-week type 1 diabetes therapy (insulin) intensification period and a 2-week placebo run-in period, and followed by a 3-week follow-up period. During the 6-week intensification period, each patient's type 1 diabetes therapy (e.g. review of blood glucose values, carbohydrate estimation, and insulin adjustment) was to be intensified in order to achieve the best standard of care based on the investigator's clinical judgment and local guidelines. The clinical management of therapy intensification and insulin intensification therefore followed a practical, real-world care approach.

Continuous glucose monitoring (CGM) was performed in all patients in EASE-2. In EASE-3, CGM assessment was performed in a substudy.

Endpoints

The primary endpoint in both trials was the change from baseline in HbA_{1c} at Week 26.

Key secondary endpoints were:

- Rate per patient-year of symptomatic hypoglycemic adverse events (AEs) with confirmed PG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemic AEs (i.e. all investigator-reported AEs that had confirmed PG <54 mg/dL [<3.0 mmol/L] with symptoms reported and all severe hypoglycemic events that were confirmed by adjudication):

  - From Week 5 to 26
  - From Week 1 to 26
- 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) as determined by CGM in Weeks 23 to 26 (EASE-2 only)
  - Interstitial glucose variability based on the interquartile range (IQR) as determined by CGM in Weeks 23 to 26 (EASE-2 only).
  - In EASE-3, CGM outcomes were reported as further endpoints and were only analyzed within a substudy in 17% of the patient population
  - Total daily insulin dose (TDID) at Week 26
  - Systolic blood pressure (SBP) at Week 26
  - Diastolic blood pressure (DBP) at Week 26

Statistical analyses

In both Phase 3 trials, the primary endpoint was analyzed using restricted maximum likelihood estimation based on mixed-effect model for repeated measures (MMRM) to obtain adjusted means for the treatment effects. The primary treatment comparisons were the Bonferroni-adjusted contrasts between the higher doses of empagliflozin (10 mg or 25 mg) and placebo, with each dose tested at the level of α=0.025 (2-sided).

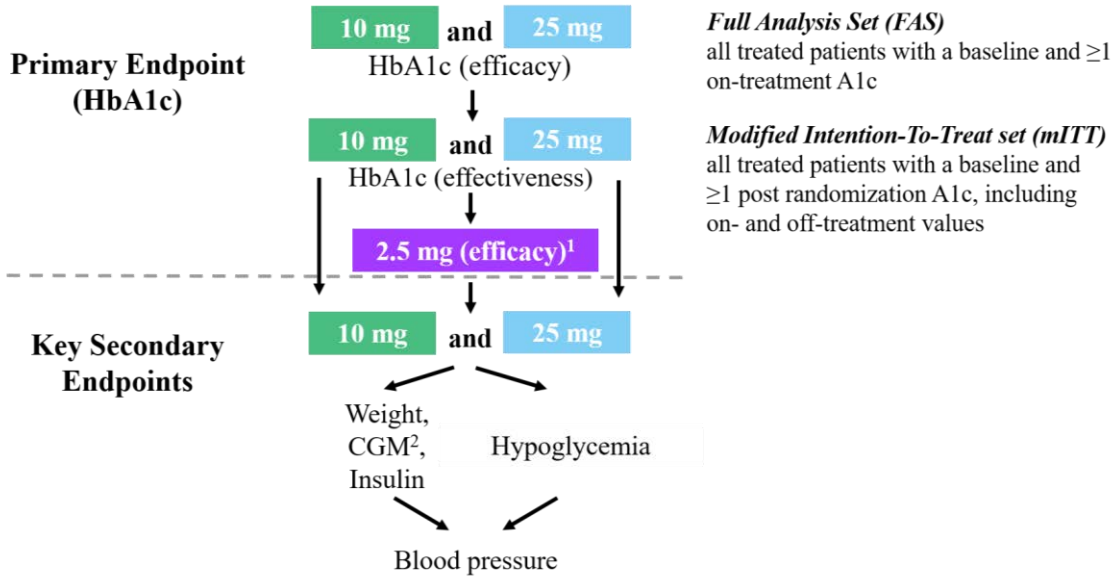
The primary efficacy analysis included on-treatment data only. It was based on the full analysis set (FAS), defined as all treated patients with a baseline and at least one on-treatment HbA_{1c} measurement, and observed cases on treatment (OC). Subsequently, an effectiveness analysis (on- and off- treatment data) was performed in a hierarchical manner, based on the modified intention-to-treat set (mITT), defined as all treated patients with a baseline and at least one post randomization HbA_{1c} measurement, and including data after treatment discontinuation (OC-AD).

FOR EASE-3: if the null hypotheses were rejected for both the efficacy and effectiveness analyses, then the primary efficacy endpoint for empagliflozin 2.5 mg versus placebo and the key secondary endpoints for the higher doses were to be tested in a confirmatory way using a gatekeeping approach with unequal splitting of the α and sequential testing (Figure 19).

FOR EASE-2: if the null hypotheses were rejected for both the efficacy and effectiveness analyses, then the key secondary endpoints were to be tested in a confirmatory way using a gatekeeping approach with unequal splitting of the α and sequential testing.

Confirmatory testing of the key secondary endpoints applied to the 10 mg and 25 mg doses, while analyses of the 2.5 mg dose were exploratory.

Figure 19 Hierarchical testing in EASE-3 and EASE-2



1 EASE-3 only
2 EASE-2 only

Safety analyses

Safety was assessed descriptively based on AEs, AEs of special interest (AESIs), and other specific AEs. In addition, clinical laboratory data, and vital signs were assessed. Independent external clinical event committees (CECs) performed central, blinded adjudication of ketoacidosis, severe hypoglycemia, cardiovascular/neurological events, and hepatic events.

Assessment of ketoacidosis

The occurrence of DKA was monitored and assessed in the EASE Phase 3 clinical development program in line with FDA recommendations. In addition, the occurrence of ketosis was analyzed.

Categories for the CEC adjudication of ketoacidosis were pre-defined based on international guidelines (ADA, European Association for the Study of Diabetes/EASD) and accepted by the FDA. The process was comprehensive as triggers for adjudication included not only investigator-reported AEs indicative of DKA but also elevated beta-hydroxybutyrate (BHB) values, with or without clinical manifestations. The CEC adjudicated events using classification criteria pre-defined in the charter. Events were adjudicated with degrees of certainty (certain ketoacidosis, potential ketoacidosis, unlikely ketoacidosis, ketosis, or as an unclassifiable event), severity (mild, moderate, severe, or not assessable), and outcome (recovered, sequelae, or fatal).

Broad search criteria were implemented to identify potential events. In addition to investigator-reported ketoacidosis events and broad predefined trigger search terms indicative of ketoacidosis

and acetonemia, all BHB values reported by the investigator or patients with a cut-off of 1.5 mmol/L, together with symptoms reported as AE, were used to identify potential ketoacidosis events. All patients received a point-of-care device capable of measuring blood glucose and BHB. Patients were educated on ketone monitoring when feeling unwell and to seek medical care in case of increased BHB (>1.5 mmol/L). This BHB threshold 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 (32).

Assessment of hypoglycemia

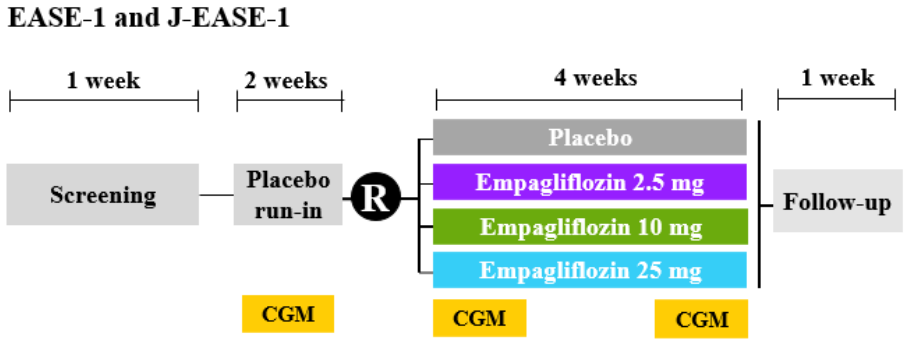
The assessment of hypoglycemia in the clinical development program was based on two distinct approaches:

1) For the purposes of the evaluation of an efficacy endpoint, investigator-reported events, classified by investigators as AEs based on their clinical review and judgment, were analyzed (including severe hypoglycemic events). All potentially severe events based on specific criteria (AE data and relevant patient-reported data in the electronic diary) were sent for independent adjudication conducted by a CEC panel following a predefined process outlined in the charter.
2) All patient-reported events with blood glucose <54 mg/dL as captured by electronic diary were analyzed and reported.

8.2.2 Phase 2 trial design

EASE-1 was a randomized, double-blind, placebo-controlled dose-finding study assessing the safety, tolerability, PK, and PD of empagliflozin 2.5 mg, 10 mg, and 25 mg administered for 4 weeks as adjunctive therapy to multiple daily injections insulin in patients with type 1 diabetes (Figure 20). J-EASE-1 had overall the same design as EASE-1 and was conducted in Japanese patients with type 1 diabetes. The primary endpoint of EASE-1 and J-EASE-1 was the change from baseline in urinary glucose excretion (UGE) after 7 days of treatment.

Figure 20 Phase 2 trial design



R: randomization; CGM: continuous glucose monitoring

The Phase 2 trial ATIRMA was an uncontrolled, open-label, 8-week pilot trial investigating the empagliflozin 25 mg dose in patients with type 1 diabetes and renal hyperfiltration.

8.3 Biopharmaceutics

A film-coated tablet formulation for oral delivery was used for empagliflozin in the clinical trials for type 1 diabetes. For the 10 and 25 mg dose strengths, the formulation is the same as the marketed formulation of empagliflozin. For the 2.5 mg dose strength, the formulation used in the clinical trials is the final formulation also proposed for commercial supply. It is almost identical to the marketed formulation for the 10 mg dose strength, i.e. the same blend is used to press the tablet cores and the tablet cores are coated using the identical non-functional film-coat and only the amount of film-coat is adjusted to the size of the tablet cores.

The dissolution profiles of empagliflozin film-coated tablets 2.5 mg, 10 mg, and 25 mg are superimposable. The same dissolution procedure and the same specification are proposed for empagliflozin film-coated tablets 2.5 mg as approved for the commercial strengths 10 mg and 25 mg.

8.4 Pharmacokinetics

No clinically relevant differences have been observed in pharmacokinetics of empagliflozin in patients with type 1 diabetes compared with healthy volunteers or patients with type 2 diabetes. Based on PK population analysis, body weight, gender, eGFR, smoking status, total daily insulin dose, total protein, and liver alkaline phosphatase did not have clinically meaningful impact on empagliflozin exposure.

In patients with type 1 diabetes, empagliflozin exposure increased proportionally with increasing dose within the dose range studies.

8.5 Patients in the EASE trials

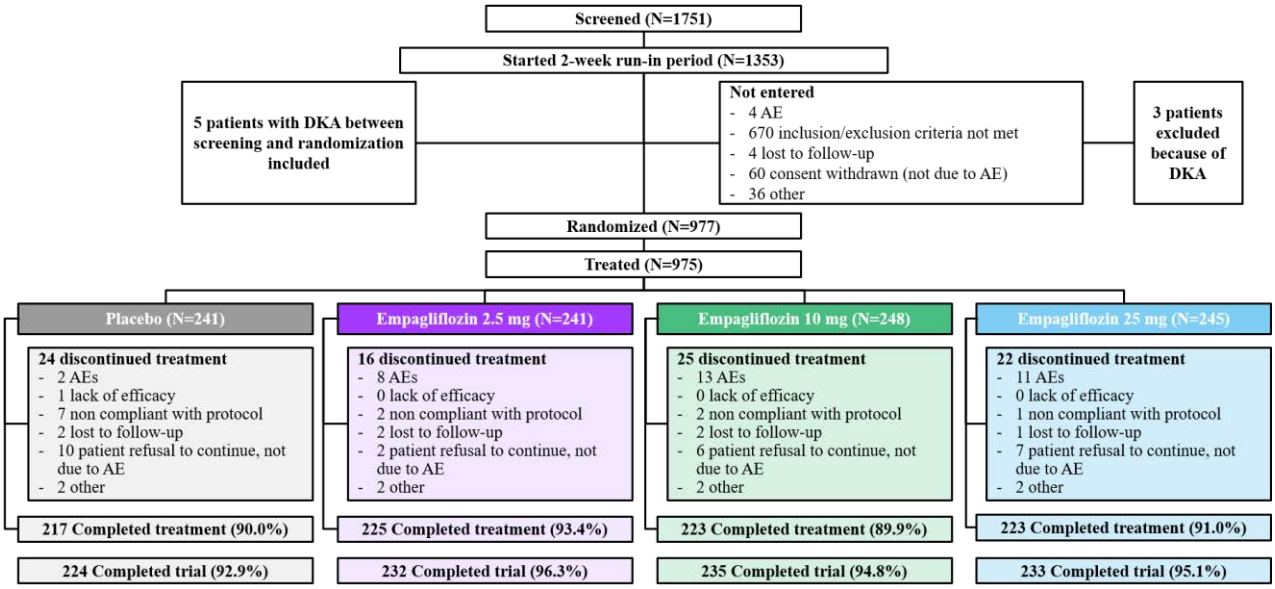
8.5.1 Patient disposition

8.5.1.1 Phase 3 trial EASE-3

In this study, 1751 patients were screened at 189 centers across 24 countries. A total of 1353 patients started the placebo run-in period, of which 977 patients entered the trial and were randomized in a 1:1:1:1 ratio to the 4 treatment groups (Figure 21).

All but 2 randomized patients were treated with trial medication. Overall, the proportion of patients that prematurely discontinued trial medication was low, and it was lower in the empagliflozin 2.5 mg group, with 93.4% of all patients completing treatment.

Figure 21 Patient disposition at Week 26 in EASE-3



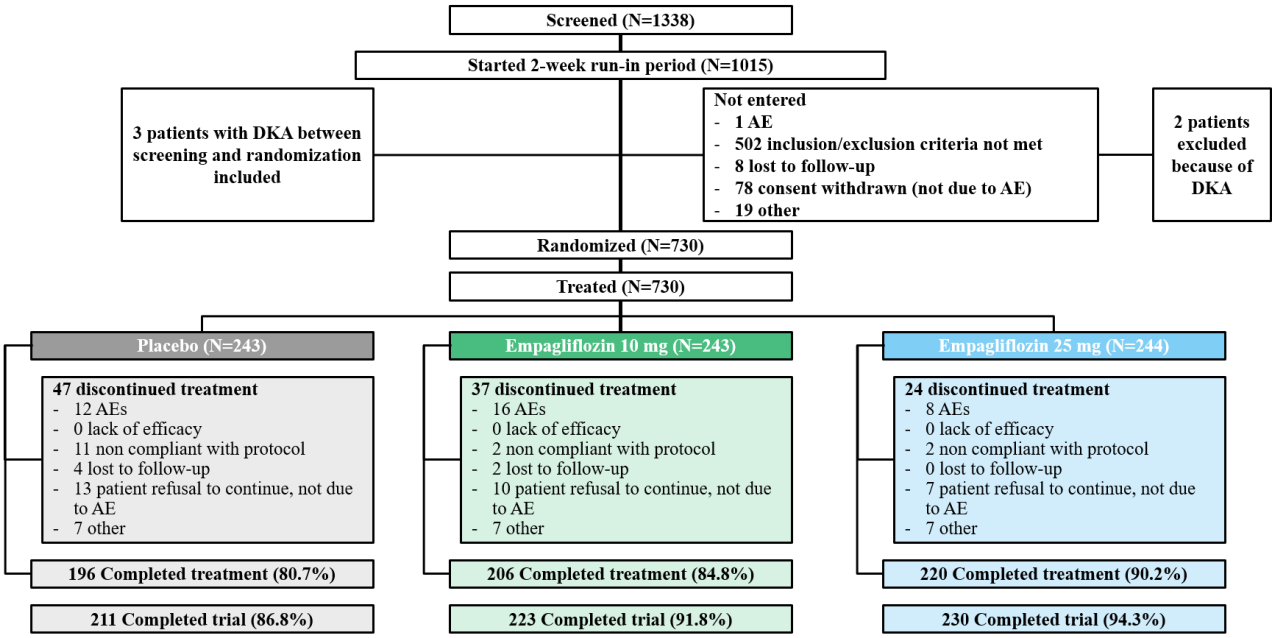
AE: adverse event

8.5.1.2 Phase 3 trial EASE-2

In this study, 1338 patients were screened at 131 centers across 17 countries. A total of 1015 patients started the placebo run-in period, of which 730 patients were entered into the trial and randomized in a 1:1:1 ratio to the 3 treatment groups (Figure 22). All randomized patients were treated with trial medication.

The proportion of patients that prematurely discontinued trial medication was low, and it was lower in the empagliflozin groups than the placebo group, both at Week 26 and at Week 52.

Figure 22 Patient disposition at Week 52 in EASE-2



AE: adverse event

8.5.1.3 Phase 2 trials (EASE 1 and J-EASE-1)

In the EASE-1 trial 75 patients were treated (placebo: 19 patients, empagliflozin 2.5 mg: 19 patients, empagliflozin 10 mg: 19 patients, empagliflozin 25 mg group: 18 patients). No patients prematurely discontinued trial medication.

In the J-EASE-1 trial 48 patients were treated (placebo: 11 patients, empagliflozin 2.5 mg: 13 patients, empagliflozin 10 mg: 12 patients, empagliflozin 25 mg group: 12 patients). One patient prematurely discontinued trial medication.

8.5.2 Demographics and baseline characteristics

8.5.2.1 Phase 3 trials

Baseline characteristics in the Phase 3 trials were balanced across the treatment groups (Tables 12 and 13), as were concomitant diagnoses and medications.

Table 12 Baseline characteristics, EASE-3

	Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg	Total
Patients in analysis set, N (%)	238 (100.0)	237 (100.0)	244 (100.0)	242 (100.0)	961 (100.0)
Sex, N (%)					
Male	114 (47.9)	118 (49.8)	114 (46.7)	123 (50.8)	469 (48.8)
Female	124 (52.1)	119 (50.2)	130 (53.3)	119 (49.2)	492 (51.2)
Race (incl. combinations), N (%)					
American Indian/Alaska Native	7 (2.9)	0	1 (0.4)	5 (2.1)	13 (1.4)
Asian	2 (0.8)	3 (1.3)	2 (0.8)	5 (2.1)	12 (1.2)
Black/African American	5 (2.1)	4 (1.7)	10 (4.1)	4 (1.7)	23 (2.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	0	0	1 (0.1)
White	223 (93.7)	233 (98.3)	232 (95.1)	228 (94.2)	916 (95.3)
Region[1], N (%)					
Europe	148 (62.2)	156 (65.8)	148 (60.7)	150 (62.0)	602 (62.6)
North America	63 (26.5)	60 (25.3)	61 (25.0)	60 (24.8)	244 (25.4)
Latin America	19 (8.0)	12 (5.1)	10 (4.1)	14 (5.8)	55 (5.7)
Pacific	5 (2.1)	7 (3.0)	12 (4.9)	11 (4.5)	35 (3.6)
Africa	3 (1.3)	2 (0.8)	13 (5.3)	7 (2.9)	25 (2.6)
Age [years], mean (SD)	42.2 (13.2)	43.4 (14.2)	42.4 (13.3)	44.2 (13.5)	43.1 (13.5)
BMI [kg/m^2], mean (SD)	27.81 (5.05)	28.02 (4.38)	28.65 (5.13)	28.41 (5.56)	28.23 (5.05)
Time since diagnosis of T1D [years], mean (SD)	21.7 (13.0)	20.8 (11.9)	20.5 (11.9)	21.2 (11.4)	21.0 (12.1)
eGFR[2] [mL/min/1.73m^2], mean (SD)	97.83 (19.32)	96.54 (19.94)	97.26 (19.91)	95.70 (19.73)	96.83 (19.71)
≥90, N (%)	161 (67.6)	154 (65.0)	168 (68.9)	162 (66.9)	645 (67.1)
60 to <90, N (%)	69 (29.0)	73 (30.8)	66 (27.0)	66 (27.3)	274 (28.5)
<60, N (%)	8 (3.4)	10 (4.2)	10 (4.1)	14 (5.8)	42 (4.4)

Full analysis set

1 Pacific region comprises Australia and New Zealand

2 Based on CKD−EPI creatinine formula

Table 13 Baseline characteristics, EASE-2

	Placebo	Empa 10 mg	Empa 25 mg	Total
Patients in analysis set, N (%)	239 (100.0)	243 (100.0)	241 (100.0)	723 (100.0)
Sex, N (%)				
Male	109 (45.6)	118 (48.6)	111 (46.1)	338 (46.7)
Female	130 (54.4)	125 (51.4)	130 (53.9)	385 (53.3)
Race (incl. combinations of races), N (%)				
American Indian or Alaska Native	0	0	0	0
Asian	8 (3.3)	6 (2.5)	10 (4.1)	24 (3.3)
Black/African American	8 (3.3)	6 (2.5)	4 (1.7)	18 (2.5)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	0	1 (0.1)
White	225 (94.1)	230 (94.7)	227 (94.2)	682 (94.3)
Region[1], N (%)				
Europe	133 (55.6)	131 (53.9)	130 (53.9)	394 (54.5)
North America	91 (38.1)	95 (39.1)	94 (39.0)	280 (38.7)
Asia	5 (2.1)	5 (2.1)	7 (2.9)	17 (2.4)
Pacific	10 (4.2)	12 (4.9)	10 (4.1)	32 (4.4)
Age, mean (SD) [years]	44.5 (13.5)	45.7 (12.5)	45.3 (13.9)	45.2 (13.3)
BMI, mean (SD) [kg/m^2]	28.54 (5.32)	29.49 (5.54)	29.50 (6.03)	29.18 (5.65)
Time since T1D diagnosis, mean (SD) [years]	22.4 (12.4)	22.8 (12.6)	22.5 (13.0)	22.6 (12.7)
eGFR[2], mean (SD) [mL/min/1.73m^2]	95.89 (18.44)	95.02 (18.10)	94.08 (18.91)	94.99 (18.47)
≥90, N (%)	160 (66.9)	154 (63.4)	148 (61.4)	462 (63.9)
60 to <90, N (%)	72 (30.1)	82 (33.7)	84 (34.9)	238 (32.9)
<60, N (%)	7 (2.9)	7 (2.9)	9 (3.7)	23 (3.2)

Full analysis set

1Asian region comprises Taiwan; Pacific region comprises Australia.

2 Based on the CKD−EPI creatinine formula

8.5.2.2 Phase 2 trials

Baseline characteristics were balanced across the treatment groups in the EASE-1 and J-EASE-1 trials. See Table 14 for an overview of the overall trial populations.

Table 14 Baseline characteristics, EASE-1 and J-EASE-1

	EASE-1	J-EASE-1
Number of patients, N (%)	75 (100.0)	48 (100.0)
Sex, N (%)		
Male	53 (70.7)	22 (45.8)
Female	22 (29.3)	26 (54.2)
Race, N (%)		
Asian	0	48 (100.0)
White	75 (100.0)	0
Age, mean (SD) [years]	41.0 (10.9)	44.8 (11.4)
BMI, mean (SD) [kg/m^2]	25.75 (3.64)	23.34 (3.19)
Time since diagnosis of T1D, mean (SD) [years]	20.0 (12.2)	16.7 (10.9)
HbA_{1c}, mean (SD) [%]	8.24 (0.69)	8.06 (0.57)
eGFR[1], mean (SD) [mL/min/1.73 m^2]	102.36 (13.82)	89.57 (14.73)

Full analysis set
1 Based on the CKD−EPI creatinine formula

8.6 Additional efficacy data

8.6.1 Phase 3 trial EASE-3

8.6.1.1 HbA_{1c}

Primary analyses

The primary efficacy analysis showed that when added to intensified insulin (treatment intensification period), empagliflozin 2.5 mg demonstrated a significant decrease in mean HbA_{1c} compared with placebo; see Table 15.

Similar results were obtained in the primary effectiveness analysis.

Table 15 Change from baseline in HbA_{1c} [%] at Week 26 in EASE-3

	Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg
Primary efficacy analysis[1]				
Patients analyzed, N	238	237	244	242
Baseline value, mean (SE)	8.19 (0.04)	8.14 (0.04)	8.19 (0.04)	8.19 (0.04)
Change from baseline, adjusted mean (SE)	0.20 (0.05)	-0.09 (0.05)	-0.25 (0.05)	-0.33 (0.05)
Comparison vs. placebo, adjusted mean (SE)		-0.28 (0.07)	-0.45 (0.07)	-0.52 (0.07)
99% CI		-0.46, -0.11	NA	NA
95% CI		-0.42, -0.15	-0.58, -0.32	-0.66, -0.39
p-value		<0.0001	<0.0001	<0.0001
Primary effectiveness analysis[2]				
Patients analyzed, N	239	239	246	245
Baseline value, mean (SE)	8.19 (0.04)	8.14 (0.04)	8.19 (0.04)	8.19 (0.04)
Change from baseline, adjusted mean (SE)	0.21 (0.05)	-0.06 (0.05)	-0.23 (0.05)	-0.30 (0.05)
Comparison vs. placebo, adjusted mean (SE)		-0.27 (0.07)	-0.44 (0.07)	-0.50 (0.07)
95% CI		-0.40, -0.14	-0.57, -0.30	-0.64, -0.37
p-value		<0.0001[3]	<0.0001	<0.0001

NA: not applicable

1 Included on-treatment data only. Mixed-effect model for repeated measures (MMRM) analysis based on FAS and observed cases (OC)

2 Included on- and off-treatment data. MMRM analysis based on modified intention-to-treat set (mITT), including data after treatment discontinuation (OC-AD)

3 Nominal

MMRM model includes baseline HbA_{1c} and baseline eGFR as linear covariates and baseline pre-existing insulin therapy, treatment, visit, visit-by-treatment, and baseline HbA_{1c}-by-visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Subgroup analyses for HbA_{1c} (EASE-3)

In addition to data provided in Section 3.1, results for all empagliflozin doses studied in EASE-3 for the subgroups 'eGFR at baseline' and 'time since diagnosis' are shown below (Figures 23 and 24).

Empagliflozin 2.5 mg would not be recommended in patients eGFR below 60 mL/min/1.73m^2.

For the subgroup 'time since diagnosis' inconsistent data were observed, leading to the conclusion that time since diagnosis has no relevant impact on HbA_{1c} reduction under empagliflozin treatment in patients with type 1 diabetes.

Figure 23 Change from baseline in HbA_{1c} at Week 26 by time since diagnosis of type 1 diabetes, EASE-3

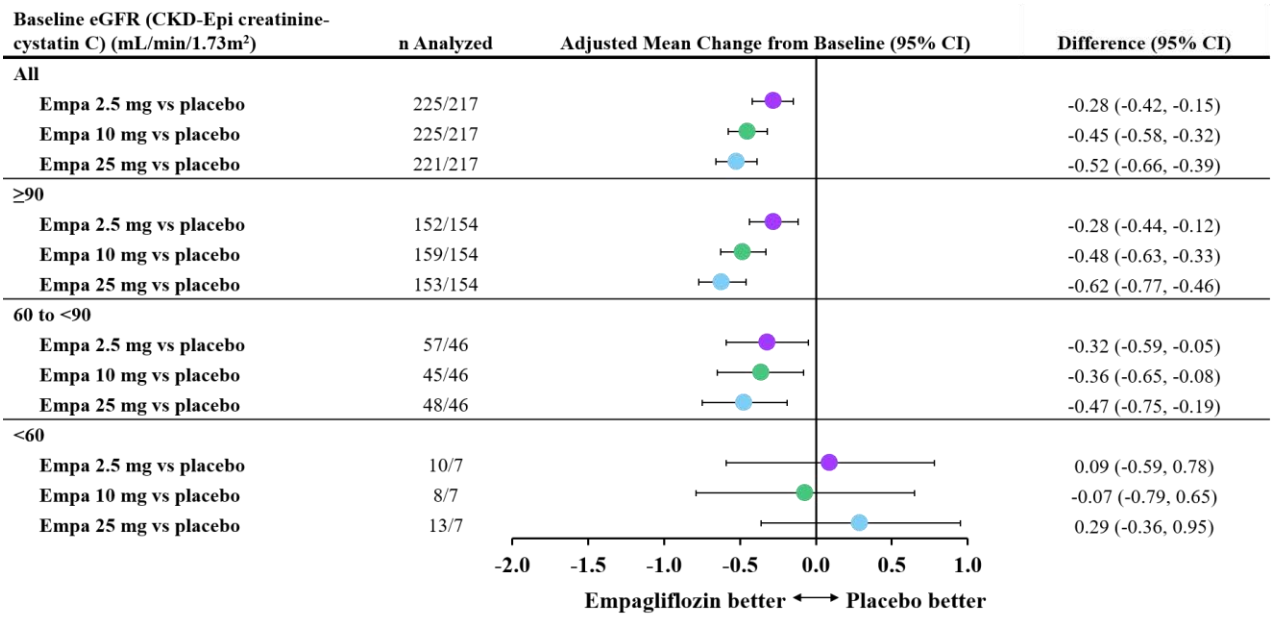
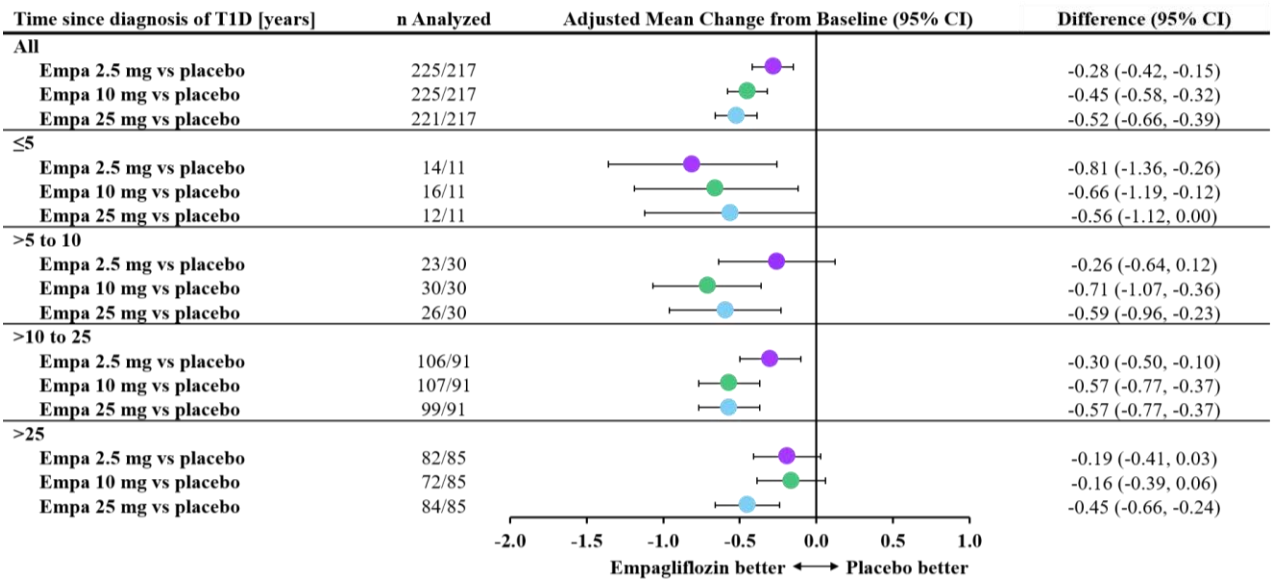


Figure 24 Change from baseline in HbA_{1c} at Week 26 by baseline eGFR in EASE-3



8.6.1.2 Key secondary and other endpoints (EASE-3)

The impact of treatment with empagliflozin beyond a reduction in HbA_{1c} were investigated as key secondary and other endpoints. The analyses for the empagliflozin 2.5 mg dose were not included

in the testing hierarchy, but treatment with this dose resulted in statistically robust and clinically significant improvements versus placebo in body weight, daily insulin requirement, and systolic blood pressure (Table 16).

Please note that the analysis of hypoglycemia as a key secondary endpoint is presented in Section 8.6.3, along with the safety endpoints of hypoglycemia.

Table 16 Overview of key secondary endpoints, change from baseline at Week 26 in EASE-3

	Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg
Patients in analysis set	238	237	244	242
Body weight [kg], FAS (OC)				
Adjusted mean change (SE)	0.21 (0.20)	-1.55 (0.20)	-2.83 (0.20)	-3.22 (0.20)
Comparison vs. placebo, adjusted mean (95% CI)		-1.76 (-2.32, -1.20)	-3.04 (-3.60, -2.48)	-3.43 (-3.99, -2.87)
99.75% CI		NA	-3.91, -2.18	-4.30, -2.57
p-value		<0.0001[2]	<0.0001	<0.0001
Total Daily Insulin Dose, FAS (OC)				
Adjusted mean change (SE) [U/kg]	-0.011 (0.007)	-0.060 (0.007)	-0.080 (0.007)	-0.102 (0.007)
Comparison vs. placebo, adjusted mean (95% CI)		-0.049 (-0.069, -0.030)	-0.070 (-0.090, -0.049)	-0.091 (-0.111, -0.071)
99.75% CI		NA	-0.101, -0.039	-0.122, -0.060
p-value		<0.0001[2]	<0.0001	<0.0001
Adjusted mean change (SE) [%]	-1.07 (0.95)	-7.44 (0.94)	-10.52 (0.97)	-13.70 (0.95)
Comparison vs. placebo, adjusted mean (95% CI)		-6.37 (-8.99, -3.76)	-9.46 (-12.11, -6.80)	-12.63 (-15.26, -10.00)
SBP [mmHg], FAS (OC-H)				
Adjusted mean change (SE)	0.4 (0.7)	-1.7 (0.7)	-3.5 (0.7)	-3.4 (0.7)
Comparison vs. placebo, adjusted mean (95% CI)		-2.1 (-3.9, -0.2)	-3.9 (-5.7, -2.1)	-3.7 (-5.6, -1.9)
99.75% CI		NA	-6.8, -1.1	-6.6, -0.9
p-value		0.0270[2]	<0.0001	<0.0001
DBP [mmHg], FAS (OC-H)				
Adjusted mean change (SE)	0.0 (0.4)	-0.4 (0.4)	-1.8 (0.4)	-1.5 (0.4)
Comparison vs. placebo, adjusted mean (95% CI)		-0.3 (-1.5, 0.9)	-1.7 (-2.9, -0.5)	-1.4 (-2.6, -0.2)
99.75% CI		NA	-3.6, 0.1	-3.3, 0.4
p-value		0.6023[2]	0.0047	0.0202

Mixed-effect model for repeated measures (MMRM) analysis based on full analysis set
OC: observed cases, OC-H: observed cases excluding data after use of antihypertensives, NA: not applicable, SBP: systolic blood pressure, DBP: diastolic blood pressure

1 Model includes baseline efficacy variable, baseline eGFR, and baseline HbA_{1c} as linear covariates, and baseline pre-existing insulin therapy, treatment, visit, visit-by-treatment-interaction, and baseline efficacy variable-by-visit interaction as fixed effects. An unstructured covariance structure was used to model the within-patient measurements.

2 Nominal p-value

8.6.1.3 Further endpoints

Continuous glucose monitoring (CGM) endpoints (EASE-3)

CGM analysis of the change from baseline in the percentage of time spent in the target glucose range of >70 to 180 mg/dL (>3.9 to 10.0 mmol/L), and the change from baseline in inter-quartile range was performed.

In EASE-3, CGM outcomes were reported as further endpoints since the analyses were performed based on data from a substudy only.

At each timepoint, an increase in the percentage of time spent in the target glucose range was observed for all empagliflozin treatment groups compared with placebo (Table 17). At Week 26, treatment with empagliflozin 2.5 mg resulted approximately in one additional hour per day in target glycemic range.

Table 17 Change from baseline in the time spent in the target glucose range (>70 to 180 mg/dL), patients in the EASE-3 CGM substudy

	Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg
Patients analyzed, N	37	41	47	39
BL value [%], mean (SE)	42.82 (1.72)	48.51 (1.68)	42.76 (2.08)	48.02 (1.45)
BL value [h/day], mean (SE)	10.28 (0.41)	11.64 (0.40)	10.26 (0.50)	11.52 (0.35)
Week 25 to 26				
Patients with value at visit, N	26	36	41	29
Value at visit [%], adjusted mean (SE)	46.19 (1.97)	50.47 (1.74)	56.83 (1.61)	53.56 (1.88)
Change from BL [%], adjusted mean (SE)	0.55 (1.97)	4.83 (1.74)	11.20 (1.61)	7.92 (1.88)
Comparison vs. placebo				
Adjusted mean (SE)		4.28 (2.63)	10.65 (2.54)	7.37 (2.73)
95% CI		-0.92, 9.48	5.63, 15.66	1.97, 12.76
Change from BL [h/day], adj. mean (SE)	0.13 (0.47)	1.16 (0.42)	2.69 (0.39)	1.90 (0.45)
Comparison vs. placebo				
Adjusted mean (SE)		1.03 (0.63)	2.55 (0.61)	1.77 (0.66)
95% CI		-0.22, 2.27	1.35, 3.76	0.47, 3.06

Mixed-effect model for repeated measures (MMRM) analysis based on FAS and observed cases excluding data after use of paracetamol

BL: baseline

MMRM model includes baseline time in the target range, baseline HbA_{1c}, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy, treatment, visit, and visit-by-treatment interaction, baseline time in the target range-by-visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Interstitial glucose variability was assessed using the interquartile range (IQR), mean amplitude of glycemic excursions (MAGE), and coefficient of variation. Change from baseline in IQR was defined as a further exploratory endpoint of efficacy for the patients taking part in the substudy. At

each time point, a decrease in IQR was observed in all empagliflozin treatment groups compared with placebo (Table 18).

Table 18 Change from baseline in IQR of glucose [mg/dL], patients in the EASE-3 CGM substudy

	Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg
Patients analyzed, N	37	41	47	39
Baseline value, mean (SE)	101.77 (3.02)	98.77 (3.69)	107.03 (3.82)	101.80 (3.57)
Week 25 to 26				
Patients with value at visit, N	26	36	41	29
Value at visit, adjusted mean (SE)	98.91 (3.68)	91.02 (3.25)	84.28 (3.03)	88.23 (3.49)
Change from baseline, adjusted mean (SE)	-3.08 (3.68)	-10.96 (3.25)	-17.71 (3.03)	-13.76 (3.49)
Comparison vs. placebo				
Adjusted mean (SE)		-7.88 (4.90)	-14.63 (4.78)	-10.68 (5.07)
95% CI		-17.57, 1.80	-24.09, -5.17	-20.70, -0.66

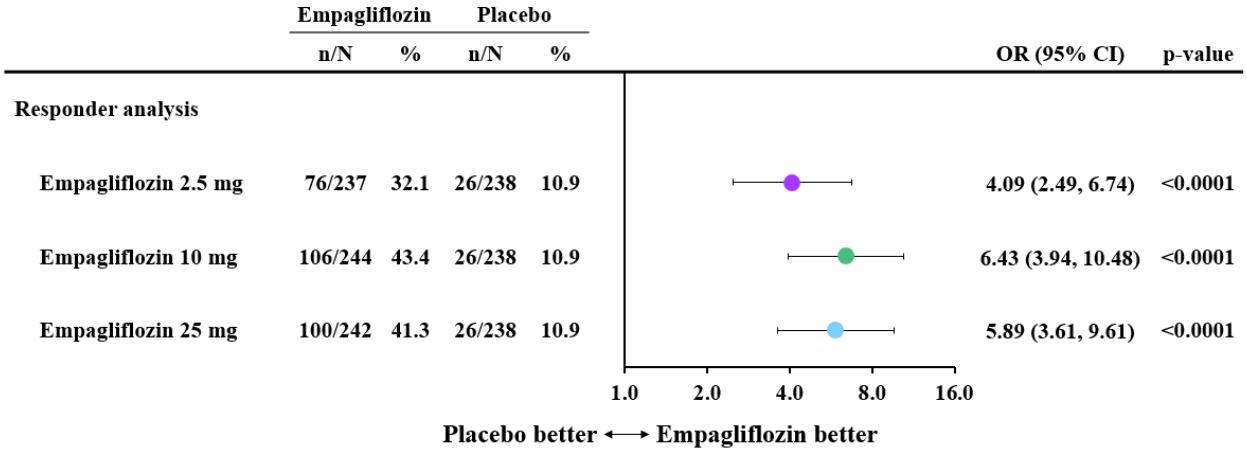
Mixed-effect model for repeated measures (MMRM) analysis based on FAS and observed cases excluding data after use of paracetamol
MMRM model includes baseline IQR of glucose, baseline HbA_{1c}, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy, treatment, visit, and visit-by-treatment interaction, baseline IQR-by-visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Responder analyses for Efficacy (EASE-3)

The relative efficacy responses for HbA_{1c} (reduction of at least 0.4%) were analyzed coupled with the absence of weight gain (no more than +2% from baseline).

Patients with this benefit were significantly more frequent in the empagliflozin treatment groups than the placebo group (Figure 25, pre-specified analysis).

Figure 25 Responder analysis for HbA_{1c} reduction from baseline by at least 0.4% without weight gain >2% at Week 26 in EASE-3



Logistic regression includes treatment, baseline pre-existing insulin therapy, baseline HbA_{1c}, baseline eGFR, and baseline weight

8.6.2 Phase 3 trial EASE-2

The efficacy results in EASE-2 were consistent with the results obtained in EASE-3. A summary of the results for the primary and key secondary endpoints is provided below.

8.6.2.1 HbA_{1c} (EASE-2)

In the primary efficacy analysis, both empagliflozin 10 mg and 25 mg demonstrated a clinically relevant and statistically significant decrease in HbA_{1c} compared with placebo that was sustained until Week 52 (Table 19 and Figure 26). Very similar results were observed in the primary effectiveness analysis and the sensitivity analyses considering the handling of missing data and the patient set tested.

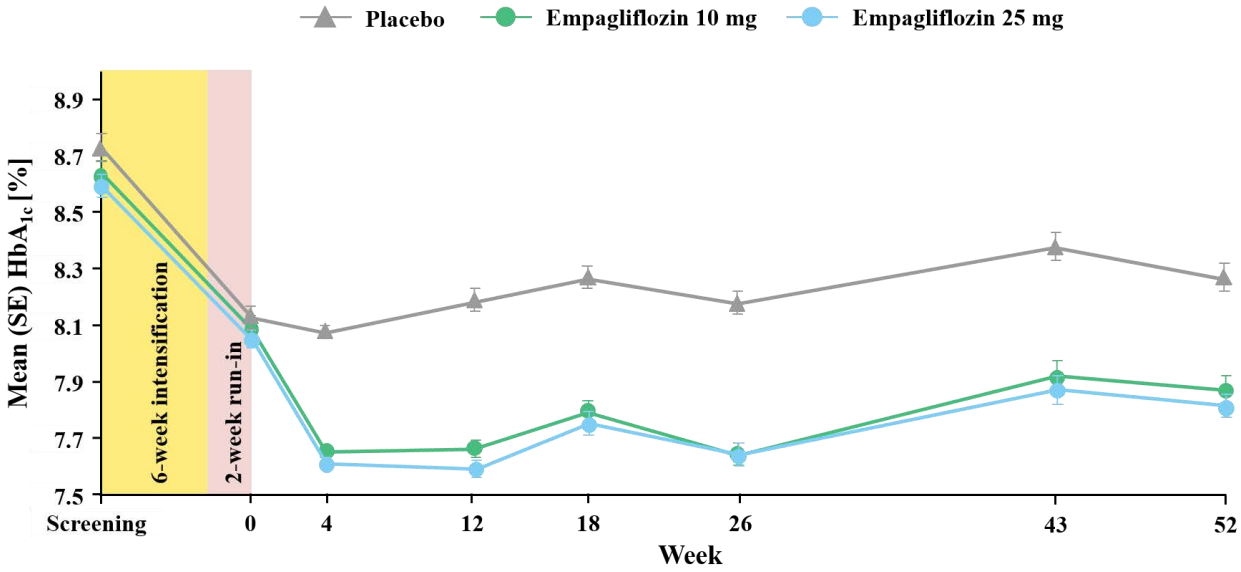
Table 19 Change from baseline in HbA_{1c} [%] in EASE-2

	Placebo	Empa 10 mg	Empa 25 mg
Patients analyzed, N	239	243	241
Baseline value, mean (SE)	8.13 (0.04)	8.10 (0.04)	8.06 (0.03)
Value at Week 26, adjusted mean (SE)	8.18 (0.04)	7.65 (0.04)	7.65 (0.04)
Change from baseline, adjusted mean (SE)	0.09 (0.04)	-0.44 (0.04)	-0.44 (0.04)
Comparison vs. placebo			
Adjusted mean (SE)		-0.54 (0.06)	-0.53 (0.06)
95% CI		-0.65, -0.42	-0.65, -0.42
p-value		<0.0001	<0.0001
Value at Week 52, adjusted mean (SE)	8.27 (0.05)	7.88 (0.05)	7.82 (0.04)
Change from baseline, adjusted mean (SE)	0.18 (0.05)	-0.21 (0.05)	-0.27 (0.04)
Comparison vs. placebo			
Adjusted mean (SE)		-0.39 (0.06)	-0.45 (0.06)
95% CI		-0.52, -0.26	-0.58, -0.32

Mixed-effect model for repeated measures (MMRM) analysis based on FAS and observed cases

MMRM model includes baseline HbA_{1c} and baseline eGFR as linear covariates and baseline pre-existing insulin therapy, treatment, visit, visit-by-treatment interaction, and baseline HbA_{1c}-by-visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

Figure 26 HbA_{1c} over time in EASE-2

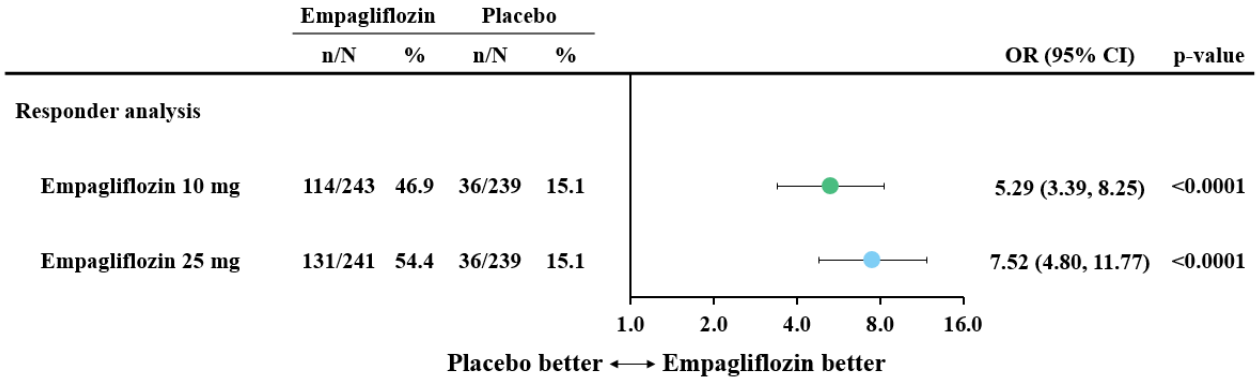


Responder analyses (EASE-2)

To determine the benefit of treatment with empagliflozin for patients with type 1 diabetes, the relative efficacy responses for HbA_{1c} (reduction of at least 0.4%) were analyzed coupled with the absence of weight gain (no more than +2% from baseline). Patients with this benefit were

significantly more frequent in the empagliflozin treatment groups than the placebo group (Figure 27).

Figure 27 Responder analysis for HbA_{1c} reduction from baseline by at least 0.4% without weight gain >2% at Week 26 in EASE-3



Logistic regression includes treatment, baseline pre-existing insulin therapy, baseline HbA_{1c}, baseline eGFR, and baseline weight

8.6.2.2 Key secondary endpoints (EASE-2)

Empagliflozin 10 mg and 25 mg provided additional clinically important and sustained benefits to patients with type 1 diabetes in terms of several key secondary outcomes (Table 20):

- Both empagliflozin doses led to a dose-dependent, clinically relevant, and statistically significant placebo-corrected reduction in body weight at Week 26. The weight loss was sustained up to Week 52.
- Both empagliflozin doses resulted in a reduction in insulin-dose requirements; the magnitude of the decrease was similar for both doses. In contrast, there was no marked reduction in insulin requirements for the patients treated with placebo.
- Clinically relevant decreases in blood pressure were associated with both empagliflozin doses.
- Patients in the empagliflozin treatment groups spent significantly more time in the target glucose range than the patients in the placebo group, as measured by CGM.
- In addition, both doses of empagliflozin significantly decreased glycemic variability (IQR) compared with placebo, with these changes persisting over 52 weeks of treatment.

Note that the analysis of hypoglycemia as a key secondary endpoint is presented in Section 8.6.3 along with the safety endpoints of hypoglycemia.

Table 20 Overview of key secondary endpoints, EASE-2

	Placebo	Empa 10 mg	Empa 25 mg
Patients in analysis set	239	243	241
Body weight [kg] change from baseline at Week 26, MMRM[1], FAS (OC)			
Adjusted mean change (SE)	-0.10 (0.21)	-2.79 (0.20)	-3.37 (0.20)
Comparison vs. placebo, adjusted mean (95% CI)		-2.69 (-3.26, -2.11)	-3.27 (-3.84, -2.70)
99.75% CI		-3.57, -1.80	-4.15, -2.39
p-value		<0.0001	<0.0001
TDID change from baseline at Week 26, MMRM[1], FAS (OC)			
Adjusted mean change (SE) [U/kg]	-0.010 (0.007)	-0.102 (0.007)	-0.100 (0.007)
Comparison vs. placebo, adjusted mean (95% CI)		-0.092 (-0.110, -0.073)	-0.090 (-0.109, -0.072)
99.75% CI		-0.121, -0.063	-0.119, -0.062
p-value		<0.0001	<0.0001
Adjusted mean change (SE) [%]	-0.50 (0.95)	-13.79 (0.92)	-13.10 (0.91)
Comparison vs. placebo, adjusted mean (95% CI)		-13.29 (-15.88, -10.70)	-12.61 (-15.19, -10.02)
SBP [mmHg] change from baseline at Week 26, MMRM[1], FAS (OC-H)			
Adjusted mean change (SE)	-0.8 (0.7)	-2.9 (0.7)	-4.5 (0.7)
Comparison vs. placebo, adjusted mean (99.75% CI)		-2.1 (-5.2, 1.0)	-3.7 (-6.8, -0.6)
p-value		0.0397	0.0003
DBP [mmHg] change from baseline at Week 26, MMRM[1], FAS (OC-H)			
Adjusted mean change (SE)	-0.3 (0.5)	-1.6 (0.5)	-2.6 (0.5)
Comparison vs. placebo, adjusted mean (95% CI)		-1.3 (-2.7, 0.0)	-2.3 (NA)
99.75% CI		NA	-4.3, -0.3
p-value		0.0457[3]	0.0006
Time in the target glucose range [%] change from baseline in Week 23 to 26, ANCOVA[2], FAS (OC-P)			
Adjusted mean change (SE)	-1.13 (0.72)	10.73 (0.71)	11.74 (0.70)
Comparison vs. placebo, adjusted mean (99.75% CI)		11.86 (8.78, 14.93)	12.87 (9.81, 15.93)
p-value		<0.0001	<0.0001

Full analysis set

SE: standard error, CI: confidence interval, OC-P: observed cases excluding data after use of paracetamol, OC-H: observed cases excluding data after use of antihypertensives, NA: not applicable, SBP: systolic blood pressure, DBP: diastolic blood pressure, TDID: total daily insulin dose

1 Mixed-effect model for repeated measures (MMRM) model includes baseline efficacy variable, baseline HbA_{1c}, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy, treatment, visit, visit-by-treatment interaction, and baseline efficacy variable-by-visit interaction as fixed effects. Patient is included as random effect. An unstructured covariance structure was used to model the within-patient measurements.

2 Analysis of covariance (ANCOVA) model includes baseline time in the target range, baseline HbA_{1c}, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects.

3 Nominal p-value

8.6.3 Hypoglycemia data (EASE-2 and EASE-3)

This section provides an overview of the hypoglycemia data in the Phase 3 trials, including both the key secondary efficacy analysis and the safety endpoints of hypoglycemia.

The key secondary endpoint of hypoglycemia was analyzed separately for EASE-2 and EASE-3.

Adjudicated severe hypoglycemia and patient-reported hypoglycemia were safety endpoints and are presented in the same manner as the other safety data: empagliflozin 2.5 mg versus placebo in the EASE-3 trial, while the 10 mg and 25 mg doses are presented pooled across both Phase 3 trials.

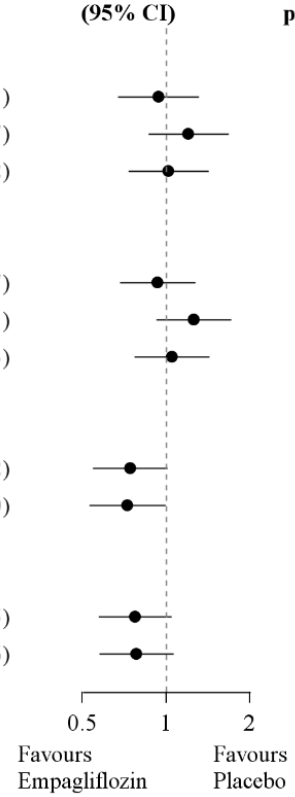
8.6.3.1.1 Key secondary endpoint

The key secondary endpoint for hypoglycemia was the rate of investigator-reported symptomatic hypoglycemic AEs with confirmed PG <54 mg/dL (<3.0 mmol/L) and/or severe hypoglycemic events confirmed by adjudication. No significant treatment difference in the rate of such events was observed between the empagliflozin groups and the placebo group for Week 5 to 26 and Week 1 to 26 (Figure 28).

The rate of events during Week 1 to 4 was similar in the empagliflozin 2.5 mg group and the placebo group, while a higher rate versus placebo was observed in the empagliflozin 10 mg group.

Figure 28 Rate of investigator-reported symptomatic hypoglycemic AEs with confirmed PG <54 mg/dL and/or severe hypoglycemic events confirmed by adjudication – negative binomial model, EASE-3 and EASE-2 – FAS (OC)

	Empagliflozin N	Empagliflozin Events n	Placebo N	Placebo Events n	Event Rate Ratio (95% CI)	p-value
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
EASE-3, Week 1-26						
Empagliflozin 2.5 mg	237	976	238	1339	0.93 (0.68,1.27)	0.6587
Empagliflozin 10 mg	244	1423	238	1339	1.26 (0.92,1.71)	0.1438
Empagliflozin 25 mg	242	1216	238	1339	1.05 (0.77,1.43)	0.7543
EASE-2, Week 5-26						
Empagliflozin 10 mg	243	1051	238	1535	0.74 (0.54,1.02)	0.0623
Empagliflozin 25 mg	239	994	238	1535	0.73 (0.53,1.00)	0.0480
EASE-2, Week 1-26						
Empagliflozin 10 mg	243	1327	239	1870	0.77 (0.57,1.05)	0.0972
Empagliflozin 25 mg	241	1333	239	1870	0.78 (0.58,1.06)	0.1180



Negative binomial model includes baseline rate of hypoglycemia, baseline HbA_{1c}, and baseline eGFR as linear covariates and baseline pre-existing insulin therapy and treatment as fixed effects. Log(time at risk [days]) was used as offset.

8.6.3.1.2 Severe hypoglycemia

There were no differences between the empagliflozin and placebo groups for CEC-confirmed severe hypoglycemic events overall, for serious events, and nocturnal events (Table 21).

This was the case both for empagliflozin 2.5 mg in EASE-3 and for the 10 mg and 25 mg doses in the pooled analysis for the Phase 3 trials.

Consistent results were obtained for investigator-defined severe hypoglycemia.

Table 21 CEC-confirmed severe hypoglycemia, EASE-3 and pooled Phase 3 trials

	EASE-3: 26 weeks		Pooled Phase 3 trials: up to 52 weeks		
	Placebo N (%)	**Empa 2.5 mg N (%)**	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with CEC-confirmed severe hypoglycemia	**6 (2.5)**	**3 (1.2)**	15 (3.1)	20 (4.1)	13 (2.7)
Serious	**4 (1.7)**	**1 (0.4)**	9 (1.9)	11 (2.2)	4 (0.8)
Fatal	**0**	**0**	0	0	0
Nocturnal[1]	**2 (0.8)**	**0**	6 (1.2)	8 (1.6)	2 (0.4)
Total number of events[2]	**6**	**9**	21	33	14
Time at risk [100-PY]	**1.15**	**1.18**	3.31	3.46	3.49
Event rate [/100-PY]	**5.22**	**7.66**	6.35	9.54	4.02

Treated set
N at risk is the number of patients with at least 1 day in the period of interest when AEs would be considered on treatment.
PY: patient years
1 Onset 0:00 to 5:59 a m.
2 One patient in the empagliflozin 2.5 mg group had 6 severe hypoglycemia events before randomization and 7 severe hypoglycemia events after randomization.

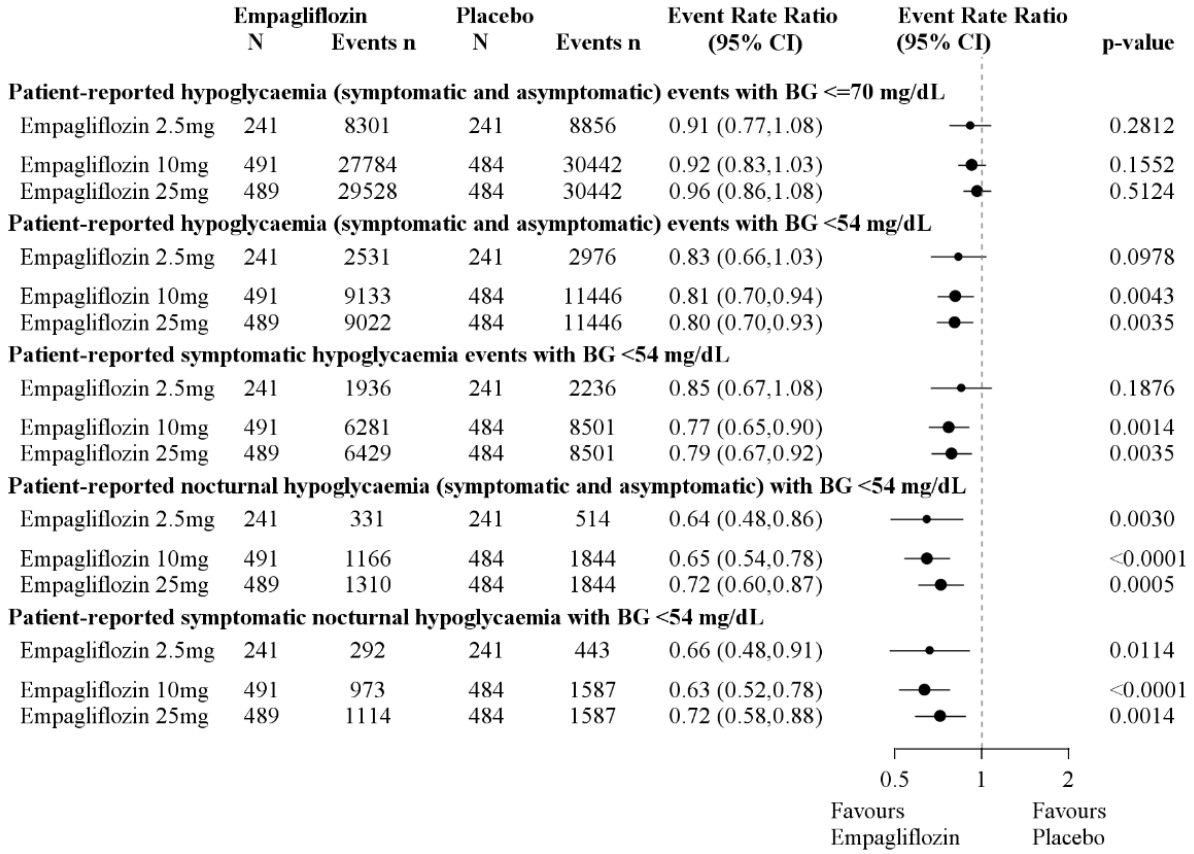
8.6.3.1.3 Patient-reported hypoglycemia

There was a significant reduction in the rate of patient-reported symptomatic and asymptomatic hypoglycemia (<54 mg/dL) with empagliflozin 10 and 25 mg up to Week 52. Empagliflozin 2.5 mg showed a similar trend in EASE-3 (Figure 29).

Frequencies of patients with patient-reported hypoglycemia were similar across the treatment groups, for overall events and nocturnal events (both symptomatic and asymptomatic). For events with PG <54 mg/dL, the rates per patient year were lower in the empagliflozin 2.5 mg group than the placebo group for nocturnal events.

Consistent with the 2.5 mg data, event rates in the empagliflozin 10 mg and 25 mg groups were lower than in the placebo group for all events and nocturnal events.

Figure 29 Rate of patient-reported hypoglycemia episodes, EASE-3 and pooled Phase 3 trials



Treated set

Model includes baseline eGFR and baseline HbA_{1c} as linear covariate and treatment, baseline pre-existing insulin therapy as fixed effect.

8.6.4 Patient-reported outcomes in EASE Phase 3 trials (EASE-2 and EASE-3)

Patient-centered healthcare is based on informed treatment choices by patients and their families in line with their individual needs, values, and preferences. In the EASE Phase 3 clinical trials, the following patient-reported outcome (PRO) instruments were used in line with FDA's 'Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims':

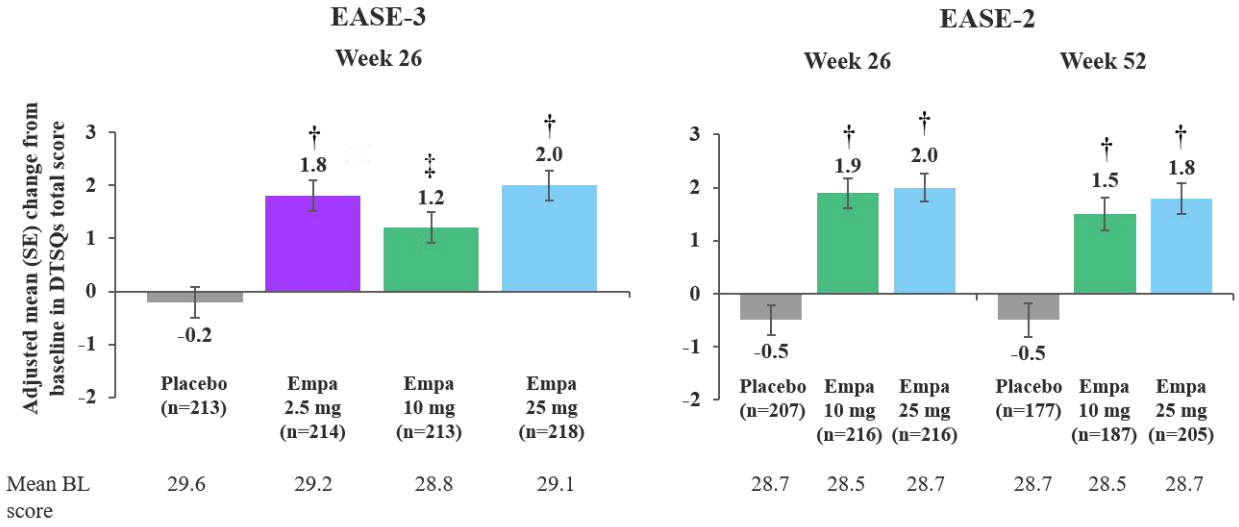
- The Diabetes Treatment Satisfaction Status Questionnaire (DTSQs), which evaluates current satisfaction with treatment. Higher total scores are associated with greater treatment satisfaction.
- The Diabetes Treatment Satisfaction Change Questionnaire (DTSQc), a retrospective recall version of the questionnaire. Higher scores are associated with greater treatment satisfaction.

Treatment comparisons were made between each randomized empagliflozin group (2.5 mg, 10 mg, and 25 mg) and placebo.

All analyses were exploratory. Descriptive statistics were summarized for every questionnaire and respective scores by treatment arm. Analysis of covariance (ANCOVA) models were conducted to evaluate differences between treatment groups in the change from baseline to Week 26 (and Week 52 in EASE-2 trial) in individual scores.

The results in both Phase-3 trials showed improvements from baseline DTSQs total score in the empagliflozin treatment groups (Figure 30). This was observed both at Week 26 and Week 52 (EASE-2). Results from the retrospective recall version of the treatment satisfaction measure, the DTSQc, was consistent with the positive effect of empagliflozin on overall treatment satisfaction (data not shown).

Figure 30 Change from baseline in DTSQs total score in EASE-2 and EASE-3



Exploratory analyses; † $p<0.001$; ‡ $p<0.01$ for difference versus control

8.7 Additional safety data

A total of 1705 patients with type 1 diabetes were treated in the Phase 3 trials EASE-3 and EASE-2. Of these, 484 were treated with placebo, 241 were treated with empagliflozin 2.5 mg, 491 were treated with empagliflozin 10 mg, and 489 were treated with empagliflozin 25 mg.

The safety data for empagliflozin 2.5 mg were analyzed in the EASE-3 trial. The largest safety dataset of the 10 and 25 mg doses pooled across the two Phase 3 trials was analyzed in order to establish the upper boundary for general safety with the 2.5 mg dose (Table 22). This pooling included all safety data analyzed up to 52 weeks.

Table 22 Numbers of treated patients in EASE-3 and EASE-2 and the pooled dataset

	Placebo	Empa 2.5 mg	Empa 10 mg	Empa 25 mg	Total
EASE-3	241	241	248	245	975
Pooled Phase 3 studies	484	0	491	489	1464
EASE-3	241	0	248	245	734
EASE-2	243	0	243	244	730

8.7.1 Exposure to study medication

In general, exposure was balanced between the empagliflozin and placebo groups (Table 23).

Trial EASE-2 had a duration of 52 weeks, whereas EASE-3 had a duration of 26 weeks. Therefore, the majority of patients (>90%) in the pooled Phase 3 trials were exposed to study medication for at least 24 weeks. Beyond 26 weeks, after which EASE-3 had stopped, there was a corresponding reduction in the number of patients in the pooled Phase 3 trials.

Table 23 Exposure to study medication, EASE-3 and pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo N (%)	**Empa 2.5 mg N (%)**	**Placebo N (%)**	**Empa 10 mg N (%)**	**Empa 25 mg N (%)**
Number of patients, N (%)	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Exposure categories, N (%)					
≥1 day	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
≥4 weeks	**236 (97.9)**	**238 (98.8)**	477 (98.6)	485 (98.8)	477 (97.5)
≥8 weeks	**232 (96.3)**	**235 (97.5)**	466 (96.3)	478 (97.4)	472 (96.5)
≥16 weeks	**224 (92.9)**	**230 (95.4)**	445 (91.9)	467 (95.1)	461 (94.3)
≥24 weeks	**218 (90.5)**	**226 (93.8)**	429 (88.6)	450 (91.6)	454 (92.8)
≥28 weeks	**3 (1.2)**	**8 (3.3)**	n.c.	n.c.	n.c.
≥32 weeks	**n.a.**	**n.a.**	208 (43.0)	222 (45.2)	228 (46.6)
≥40 weeks	**n.a.**	**n.a.**	203 (41.9)	215 (43.8)	226 (46.2)
≥46 weeks	**n.a.**	**n.a.**	200 (41.3)	209 (42.6)	225 (46.0)
≥54 weeks	**n.a.**	**n.a.**	9 (1.9)	6 (1.2)	6 (1.2)
Duration of exposure [days]					
Mean (SD)	**173.2 (35.9)**	**177.1 (29.7)**	248.6 (105.5)	256.2 (100.2)	259.4 (103.4)
Median	**183.0**	**183.0**	187.0	190.0	190.0
Range	**(4, 203)**	**(3, 206)**	(4, 386)	(5, 415)	(1, 396)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2

Treated set, on-treatment analysis
n.c. = not calculated; n.a. = not applicable

8.7.2 Adverse events

8.7.2.1 Overview of adverse events

Overall, adverse events occurred with similar frequency among the treatment arms (Table 24).

Table 24 Overview of patients with adverse events, EASE-3 and pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo N (%)	Empa 2.5 mg N (%)	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with any AE	**203 (84.2)**	**194 (80.5)**	433 (89.5)	441 (89.8)	428 (87.5)
Severe	**9 (3.7)**	**12 (5.0)**	29 (6.0)	48 (9.8)	41 (8.4)
Investigator-defined drug-related	**56 (23.2)**	**70 (29.0)**	158 (32.6)	221 (45.0)	226 (46.2)
Other significant AEs (ICH E3)	**2 (0.8)**	**4 (1.7)**	11 (2.3)	19 (3.9)	13 (2.7)
Leading to treatment discontinuation	**2 (0.8)**	**8 (3.3)**	14 (2.9)	29 (5.9)	18 (3.7)
Serious	**16 (6.6)**	**13 (5.4)**	44 (9.1)	64 (13.0)	42 (8.6)
Fatal	**0**	**0**	0	0	1 (0.2)
Immediately life-threatening	**1 (0.4)**	**1 (0.4)**	4 (0.8)	7 (1.4)	4 (0.8)
Disability/incapacity	**0**	**1 (0.4)**	0	0	0
Requiring hospitalization	**9 (3.7)**	**9 (3.7)**	26 (5.4)	49 (10.0)	30 (6.1)
Prolonging hospitalization	**0**	**0**	0	3 (0.6)	2 (0.4)
Other	**7 (2.9)**	**5 (2.1)**	19 (3.9)	16 (3.3)	11 (2.2)

Treated set, on-treatment analysis

8.7.2.2 Common adverse events

All adverse events

Most AEs were reported within the system organ class metabolism and nutrition disorders, and the most common AE at preferred-term (PT) level was hypoglycemia, reported with similar frequency in all treatment groups (Table 25).

Among the metabolism and nutrition disorders, the PTs diabetic ketoacidosis and ketoacidosis were reported more frequently for patients in the empagliflozin 10 mg and 25 mg groups than in the placebo group. Such an increase versus placebo was not observed in EASE-3 for empagliflozin 2.5 mg.

Other PTs that were reported with notably higher frequencies for empagliflozin than placebo were vomiting, nausea, diarrhea, increased blood ketone body, polyuria, and pollakiuria. The increased

frequency of pollakiuria was noted in the empagliflozin 10 mg and 25 mg groups, but not the empagliflozin 2.5 mg group.

Table 25 Patients with adverse events with a frequency of >2% in any treatment group at preferred term level in EASE-3 and pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
System organ class Preferred term	Placebo	Empa 2.5 mg	Placebo	Empa 10 mg	Empa 25 mg
Number of patients	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with any AE, N (%)	**203 (84.2)**	**194 (80.5)**	433 (89.5)	441 (89.8)	428 (87.5)
Metabolism and nutrition disorders	**153 (63.5)**	**142 (58.9)**	314 (64.9)	343 (69.9)	321 (65.6)
Hypoglycemia	**146 (60.6)**	**137 (56.8)**	299 (61.8)	318 (64.8)	298 (60.9)
Ketosis	**4 (1.7)**	**5 (2.1)**	14 (2.9)	20 (4.1)	26 (5.3)
Diabetic ketoacidosis	**2 (0.8)**	**2 (0.8)**	6 (1.2)	18 (3.7)	13 (2.7)
Hyperglycemia	**4 (1.7)**	**1 (0.8)**	10 (2.1)	7 (1.4)	6 (1.2)
Infections and infestations	**86 (35.7)**	**83 (34.4)**	231 (47.7)	237 (48.3)	225 (46.0)
Nasopharyngitis	**24 (10.0)**	**23 (9.5)**	65 (13.4)	74 (15.1)	69 (14.1)
Urinary tract infection	**12 (5.0)**	**12 (5.0)**	41 (8.5)	46 (9.4)	36 (7.4)
Upper respiratory tract infection	**5 (2.1)**	**6 (2.5)**	30 (6.2)	25 (5.1)	35 (7.2)
Influenza	**9 (3.7)**	**5 (2.1)**	20 (4.1)	29 (5.9)	20 (4.1)
Gastroenteritis	**5 (2.1)**	**3 (1.2)**	11 (2.3)	18 (3.7)	13 (2.7)
Sinusitis	**5 (2.1)**	**6 (2.5)**	18 (3.7)	17 (3.5)	13 (2.7)
Bronchitis	**7 (2.9)**	**3 (1.2)**	16 (3.3)	12 (2.4)	10 (2.0)
Vulvovaginal mycotic infection	**3 (1.2)**	**4 (1.7)**	5 (1.0)	14 (2.9)	15 (3.1)
Pharyngitis	**8 (3.3)**	**4 (1.7)**	10 (2.1)	7 (1.4)	10 (2.0)
Fungal infection	**0**	**1 (0.4)**	7 (1.4)	10 (2.0)	14 (2.9)
Gastrointestinal disorders	**21 (8.7)**	**26 (10.8)**	70 (14.5)	91 (18.5)	97 (19.8)
Vomiting	**4 (1.7)**	**6 (2.5)**	16 (3.3)	29 (5.9)	18 (3.7)
Nausea	**4 (1.7)**	**7 (2.9)**	18 (3.7)	21 (4.3)	26 (5.3)
Diarrhea	**1 (0.4)**	**4 (1.7)**	10 (2.1)	17 (3.5)	15 (3.1)
Investigations	**12 (5.0)**	**18 (7.5)**	45 (9.3)	70 (14.3)	69 (14.1)
Blood ketone body increased	**3 (1.2)**	**4 (1.7)**	13 (2.7)	34 (6.9)	30 (6.1)

Treated set, on-treatment analysis

Table continued below

Table 25 (cont'd) Patients with adverse events with a frequency of >2% in any treatment group at preferred term level in EASE-3 and pooled Phase 3 trials

System organ class Preferred term	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo	Empa 2.5 mg	Placebo	Empa 10 mg	Empa 25 mg
Musculoskeletal and connective tissue disorders	**24 (10.0)**	**14 (5.8)**	74 (15.3)	71 (14.5)	66 (13.5)
Back pain	**1 (0.4)**	**3 (1.2)**	8 (1.7)	14 (2.9)	17 (3.5)
Musculoskeletal pain	**0**	**0**	5 (1.0)	8 (1.6)	13 (2.7)
Arthralgia	**2 (0.8)**	**3 (1.2)**	8 (1.7)	13 (2.6)	3 (0.6)
Pain in extremity	**4 (1.7)**	**1 (0.4)**	10 (2.1)	4 (0.8)	5 (1.0)
Renal and urinary disorders	**12 (5.0)**	**15 (6.2)**	26 (5.4)	38 (7.7)	53 (10.8)
Polyuria	**1 (0.4)**	**6 (2.5)**	1 (0.2)	18 (3.7)	13 (2.7)
Pollakiuria	**2 (0.8)**	**2 (0.8)**	4 (0.8)	11 (2.2)	12 (2.5)
Skin and subcutaneous tissue disorders	**10 (4.1)**	**12 (5.0)**	41 (8.5)	28 (5.7)	51 (10.4)
Rash	**5 (2.1)**	**0**	10 (2.1)	7 (1.4)	5 (1.0)
Nervous system disorders	**16 (6.6)**	**19 (7.9)**	52 (10.7)	49 (10.0)	55 (11.2)
Headache	**10 (4.1)**	**7 (2.9)**	17 (3.5)	17 (3.5)	21 (4.3)
General disorders and administration site conditions	**12 (5.0)**	**16 (6.6)**	32 (6.6)	46 (9.4)	46 (9.4)
Fatigue	**5 (2.1)**	**3 (1.2)**	12 (2.5)	12 (2.4)	8 (1.6)
Thirst	**1 (0.4)**	**5 (2.1)**	1 (0.2)	3 (0.6)	12 (2.5)
Respiratory, thoracic and mediastinal disorders	**11 (4.6)**	**10 (4.1)**	44 (9.1)	34 (6.9)	37 (7.6)
Cough	**1 (0.4)**	**3 (1.2)**	10 (2.1)	10 (2.0)	8 (1.6)
Oropharyngeal pain	**1 (0.4)**	**6 (2.5)**	10 (2.1)	6 (1.2)	10 (2.0)
Psychiatric disorders	**9 (3.7)**	**3 (1.2)**	24 (5.0)	14 (2.9)	14 (2.9)
Anxiety	**6 (2.5)**	**1 (0.4)**	10 (2.1)	3 (0.6)	5 (1.0)

Treated set, on-treatment analysis

Adverse events leading to premature discontinuation of study medication

The frequency of patients with AEs leading to discontinuation of study medication was low in the Phase 3 trials, with numerically higher frequencies reported in the empagliflozin treatment groups (Table 26).

In the pooled Phase 3 trials, the imbalance was largely driven by diabetic ketoacidosis, ketoacidosis, and blood ketone body increase.

In the empagliflozin 2.5 mg treatment group, no PT was reported for more than 1 patient.

Table 26 Patients with adverse events leading to treatment discontinuation with a frequency of >0.5% in any treatment group at preferred term level in EASE-3 and pooled Phase 3 trials

System organ class Preferred term	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo	Empa 2.5 mg	Placebo	Empa 10 mg	Empa 25 mg
Number of patients, N (%)	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with any AE leading to treatment discontinuation, N (%)	**2 (0.8)**	**8 (3.3)**	14 (2.9)	29 (5.9)	18 (3.7)
Metabolism and nutrition disorders	**0**	**3 (1.2)**	2 (0.4)	10 (2.0)	5 (1.0)
Diabetic ketoacidosis	**0**	**1 (0.4)**	2 (0.4)	5 (1.0)	4 (0.8)
Ketoacidosis	**0**	**0**	0	3 (0.6)	0
Investigations	**0**	**0**	0	5 (1.0)	4 (0.8)
Blood ketone body increased	**0**	**0**	0	4 (0.8)	2 (0.4)

Treated set, on-treatment analysis

Drug-related adverse events

Drug-related AEs as assessed by the investigator were reported for higher proportions of patients in the empagliflozin treatment groups than in the placebo groups (Table 27). This was mainly due to an imbalance in the frequencies of ketone-related events, genital infections, pollakiuria, and polyuria.

Table 27 Patients with investigator-defined drug-related adverse events with a frequency of >1% in any treatment group at preferred term level in EASE-3 and pooled Phase 3 trials

System organ class Preferred term	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo	Empa 2.5 mg	Placebo	Empa 10 mg	Empa 25 mg
Number of patients, N (%)	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with investigator-defined drug-related AEs, N (%)	**56 (23.2)**	**70 (29.0)**	158 (32.6)	221 (45.0)	226 (46.2)
Metabolism and nutrition disorders	**42 (17.4)**	**53 (22.0)**	110 (22.7)	147 (29.9)	139 (28.4)
Hypoglycemia	**40 (16.6)**	**49 (20.3)**	106 (21.9)	124 (25.3)	117 (23.9)
Ketosis	**0**	**4 (1.7)**	5 (1.0)	12 (2.4)	17 (3.5)
Diabetic ketoacidosis	**0**	**1 (0.4)**	1 (0.2)	12 (2.4)	9 (1.8)
Ketoacidosis	**0**	**1 (0.4)**	0	7 (1.4)	1 (0.2)
Infections and infestations	**10 (4.1)**	**12 (5.0)**	42 (8.7)	72 (14.7)	72 (14.7)
Urinary tract infection	**5 (2.1)**	**7 (2.9)**	23 (4.8)	27 (5.5)	24 (4.9)
Vulvovaginal mycotic infection	**3 (1.2)**	**3 (1.2)**	5 (1.0)	11 (2.2)	13 (2.7)
Fungal infection	**0**	**1 (0.4)**	4 (0.8)	10 (2.0)	11 (2.2)
Vulvovaginal candiasis	**0**	**0**	0	9 (1.8)	9 (1.8)
Genital candiasis	**0**	**0**	0	5 (1.0)	7 (1.4)
Vaginal infection	**1 (0.4)**	**0**	2 (0.4)	2 (0.4)	7 (1.4)
Genital infection fungal	**1 (0.4)**	**1 (0.4)**	4 (0.8)	6 (1.2)	4 (0.8)
Nervous system disorders	**2 (0.8)**	**5 (2.1)**	6 (1.2)	8 (1.6)	9 (1.8)
Dizziness	**1 (0.4)**	**2 (0.8)**	2 (0.4)	3 (0.6)	6 (1.2)
Headache	**1 (0.4)**	**3 (1.2)**	1 (0.2)	4 (0.8)	2 (0.4)
Gastrointestinal disorders	**2 (0.8)**	**4 (1.7)**	10 (2.1)	11 (2.2)	16 (3.3)
Nausea	**1 (0.4)**	**2 (0.8)**	4 (0.8)	6 (1.2)	7 (1.4)
Renal and urinary disorders	**6 (2.5)**	**9 (3.7)**	13 (2.7)	31 (6.3)	32 (6.5)
Polyuria	**1 (0.4)**	**4 (1.7)**	1 (0.2)	17 (3.5)	11 (2.2)
Pollakiuria	**2 (0.8)**	**2 (0.8)**	4 (0.8)	11 (2.2)	10 (2.0)
Reproductive system and breast disorders	**0**	**2 (0.8)**	1 (0.2)	8 (1.6)	13 (2.7)
Balanoposthitis	**0**	**1 (0.4)**	0	3 (0.6)	6 (1.2)
General disorders and administration site conditions	**1 (0.4)**	**5 (2.1)**	5 (1.0)	11 (2.2)	13 (2.7)
Thirst	**0**	**4 (1.7)**	0	3 (0.6)	10 (2.0)
Investigations	**5 (2.1)**	**4 (1.7)**	14 (2.9)	33 (6.7)	36 (7.4)
Blood ketone body increased	**3 (1.2)**	**2 (0.8)**	9 (1.9)	26 (5.3)	19 (3.9)

Treated set, on-treatment analysis

Serious adverse events

In trial EASE-3, the frequencies of patients with SAEs were balanced between the empagliflozin 2.5 mg and placebo groups.

In the pooled Phase 3 trials, the frequency of patients with SAEs was higher in the empagliflozin 10 mg group than in the placebo and empagliflozin 25 mg groups, largely driven by the PTs diabetic ketoacidosis and ketoacidosis (Table 28).

Table 28 Patients with serious adverse events with a frequency of >0.5% in any treatment group at preferred term level in EASE-3 and pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
System organ class Preferred term	Placebo	Empa 2.5 mg	Placebo	Empa 10 mg	Empa 25 mg
Number of patients	**241 (100.0)**	**241 (100.0)**	484 (100.0)	491 (100.0)	489 (100.0)
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with serious AEs	**16 (6.6)**	**13 (5.4)**	44 (9.1)	64 (13.0)	42 (8.6)
Metabolism and nutrition disorders	**7 (2.9)**	**7 (2.9)**	22 (4.5)	41 (8.4)	26 (5.3)
Diabetic ketoacidosis	**2 (0.8)**	**2 (0.8)**	6 (1.2)	18 (3.7)	13 (2.7)
Hypoglycemia	**4 (1.7)**	**3 (1.2)**	10 (2.1)	12 (2.4)	3 (0.6)
Ketoacidosis	**1 (0.4)**	**1 (0.4)**	3 (0.6)	7 (1.4)	4 (0.8)
Ketosis	**0**	**1 (0.4)**	1 (0.2)	0	3 (0.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2 (0.8)**	**2 (0.8)**	3 (0.6)	1 (0.2)	1 (0.2)
Basal cell carcinoma	**2 (0.8)**	**1 (0.4)**	2 (0.4)	0	0
Cardiac disorders	**0**	**2 (0.8)**	1 (0.2)	2 (0.4)	2 (0.4)
Angina unstable	**0**	**2 (0.8)**	0	0	0
Infections and infestations	**2 (0.8)**	**1 (0.4)**	3 (0.6)	8 (1.6)	7 (1.4)
Pneumonia	**0**	**0**	0	0	3 (0.6)

Treated set, on-treatment analysis

8.7.2.3 Overview of adverse events of interest

For most AESIs and other specific AEs there were similar frequencies in the empagliflozin 2.5 mg group and the placebo group (see Section 4.1).

Details regarding diabetic ketoacidosis, genital infection, urinary tract infection, are provided below in Sections 8.7.2.4 and 8.7.2.5. The results for hypoglycemia are presented in Section 8.6.3.

8.7.2.4 DKA and ketosis

Risk mitigation measures in the Phase 3 trials

Investigators were reminded that, due to the mechanism of action, patients receiving empagliflozin were at risk to underestimate their need for insulin in case of blood sugar levels within their individual target range. Insulin deficiency might lead to DKA, which could be life-threatening if not recognized and appropriately treated. All patients were made aware of this risk and were instructed not to reduce their insulin intake below investigator recommendations.

Investigators were reminded about the atypical presentation (i.e., with blood glucose lower than expected) of DKA under SGLT2 inhibitor use. As mentioned above, patients were equipped with blood BHB meters and were reminded to test their ketones in case of any symptoms of DKA, e.g., nausea, vomiting, abdominal pain etc., irrespective of the glucose value. Patients were reminded about the signs and symptoms of DKA, on the interpretation of ketone values measured via the meter, and on appropriate action to take in the event of increased ketone levels (see above).

In the same way as during routine clinical care, patients were reminded to test for ketones in case of repeatedly elevated blood glucose levels (e.g., >200–240 mg/dL [>11.1–13.3 mmol/L]) which cannot be explained. Regular (e.g., 2–3 times a week) measurements before breakfast were recommended throughout the trial from Visit 2. More frequent (e.g., once daily) measurements before breakfast were recommended during the run-in period and during the first 4 weeks of the treatment period and beyond if agreed upon with the patient afterwards and if deemed necessary by the investigator.

In the event of increased ketones (i.e., blood BHB >0.5 mmol/L), patients were to follow the rules given by their investigator (e.g., increased fluid intake and/or insulin bolus; food intake and insulin bolus in case of near-normal blood glucose) or contact their trial site. In case of deteriorating ketosis, blood glucose and ketone levels were to be checked every 1–2 hours until they were back in a range considered to be normal for the patient. Patients were instructed to immediately refer themselves to hospital and/or the Investigator, or to contact an emergency physician, in case of a blood ketone concentration >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.

In case of a suspected DKA, the investigator was to ensure that appropriate tests were performed at the earliest opportunity according to local guidelines, such as a blood gas test (pH, bicarbonate). During the conduct of the trials, an information card about DKA was introduced. The patients were asked to carry this card with them at all times and to present the card to any treating physician or healthcare professional to recognize that they may not be familiar with trial procedures and may not recognize that SGLT2 inhibitors may modify the presentation of DKA (e.g., DKA with blood glucose <250 mg/dL possible).

8.7.2.4.1 Adjudicated DKA

No cases were adjudicated as unclassifiable.

The proportion of patients with certain or potential ketoacidosis confirmed by CEC adjudication and the event rate was low and balanced in the empagliflozin 2.5 mg and placebo groups of EASE-3 (Table 29). In the pooled Phase 3 trials, the proportion of patients experiencing DKA and the event rate was higher in the empagliflozin 10 mg and 25 mg treatment groups than in the placebo group. An increase in ketosis was seen with all empagliflozin doses, but the increase relative to placebo was lower with the 2.5 mg dose than with the higher doses.

Table 29 Patients with CEC-adjudicated ketoacidosis in EASE-3 and pooled Phase 3 trials

	EASE-3 (26 weeks)		Pooled Phase 3 trials (up to 52 weeks)		
	Placebo	**Empa 2.5 mg**	**Placebo**	**Empa 10 mg**	**Empa 25 mg**
Number of patients, N (100%)	**241**	**241**	484	491	489
Total exposure [years]	**114.3**	**116.9**	329.4	344.4	347.2
Patients with adjudicated ketoacidosis events:					
Certain ketoacidosis, N (%)	**3 (1.2)**	**2 (0.8)**	6 (1.2)	21 (4.3)	16 (3.3)
Number of episodes (rate per 100 PY)	**3 (2.52)**	**2 (1.65)**	6 (1.77)	21 (5.94)	18 (5.05)
Potential ketoacidosis, N (%)	**1 (0.4)**	**3 (1.2)**	6 (1.2)	15 (3.1)	13 (2.7)
Number of episodes (rate per 100 PY)	**1 (0.84)**	**3 (2.47)**	6 (1.77)	16 (4.52)	14 (3.93)
Certain or potential ketoacidosis, N (%)	**4 (1.7)**	**4 (1.7)**	11 (2.3)	33 (6.7)	28 (5.7)
Number of episodes (rate per 100 PY)	**4 (3.36)**	**5 (4.12)**	12 (3.54)	37 (10.46)	32 (8.97)
Unlikely ketoacidosis, N (%)	**1 (0.4)**	**0**	2 (0.4)	5 (1.0)	3 (0.6)
Number of episodes (rate per 100 PY)	**1 (0.84)**	**0**	2 (0.59)	5 (1.41)	3 (0.84)
Ketosis, N (%)	**2 (0.8)**	**7 (2.9)**	8 (1.7)	33 (6.7)	28 (5.7)
Number of episodes (rate per 100 PY)	**2 (1.68)**	**8 (6.58)**	10 (2.95)	42 (11.87)	40 (11.22)
Unclassifiable case, N (%)	**0**	**0**	0	0	0

Treated set, on-treatment analysis
PY: patient years
A patient could be counted in more than one adjudication result category.

The severity of DKA events adjudicated as 'certain' or 'potential' is presented in Table 30 below.

Table 30 Severity of adjudicated DKA in EASE-3

	EASE-3 (26 weeks)		Pooled Phase 3 trials: up to 52 weeks		
	Placebo	Empa 2.5 mg	Placebo	Empa 10 mg	Empa 25 mg
Number of patients, N (100%)	**241**	**241**	484	491	489
Patients with certain or potential DKA, N (%)	**4 (1.7)**	**4 (1.7)**	11 (2.3)	33 (6.7)	28 (5.7)
Number of events (rate per 100 PY)	**4 (3.36)**	**5 (4.12)**	12 (3.54)	37 (10.46)	32 (8.97)
Events by severity					
Severe	**1**	**0**	1	2	6
Moderate	**1**	**0**	4	13	8
Mild	**2**	**5**	7	22	18
Events leading to discontinuation	**0**	**1**	1	9	4
Events leading to hospitalization	**2**	**2**	5	18	13
Outcome of event					
Fatal	**0**	**0**	0	0	1

Treated set, on-treatment analysis

Summary of the fatal event on empagliflozin 25 mg

One patient in the empagliflozin 25 mg group died from cerebral edema during treatment for DKA. This was a 28-year-old female patient on insulin pump from Poland with type 1 diabetes since 4 years of age.

106 days after randomization, the patient experienced flu-like symptoms, sinusitis, high ketones (BHB 4.6 mmol/L) and moderately increased blood glucose values (245 mg/dL). As per protocol, patient was instructed to drink fluids and to control ketones and blood glucose.

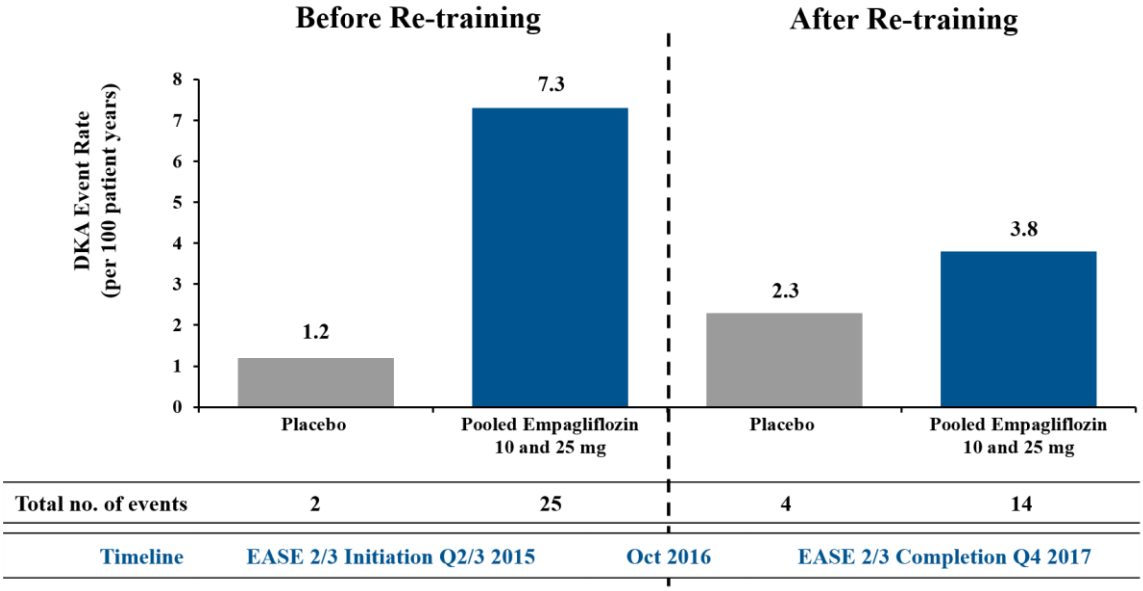
On day 4 of her illness, patient had BHB readings of 6.3 mmol/L and blood glucose of 190 mg/dL, and she visited the emergency room due to emesis and sinusitis. The patient did not inform the emergency room physician about high BHB or participation in the study and was sent home with symptomatic treatment.

In the evening, paramedics were called due to vomiting and abdominal pain. At that time blood glucose was 337 mg/dL. The patient refused to be hospitalized despite clinical advice.

On Day 5 of her illness, the last day of study medication intake, the patient was admitted to hospital with severe acidosis and hyperglycemia (500 mg/dL). Therapy included intensive hydration and insulin infusion (with normalization of blood glucose within 4 hours). In the evening, the patient developed bradycardia followed by a cardiac arrest. The patient died after the second resuscitation attempt on due to circulatory-respiratory failure secondary to DKA with cerebral edema.

Following the occurrence of the fatal case, investigators and patients were re-trained on the risk of DKA, including atypical presentation. A Trial Information Card was implemented. Patients were instructed to always carry this card and to present the card to any treating physician who may not recognize that SGLT2 inhibitors can modify the presentation of DKA. After re-training and implementation of the Trial Information Card, a decrease in the rate of DKA events with empagliflozin 10 and 25 mg doses was observed (Figure 31).

Figure 31 DKA event rate with empagliflozin 10 and 25 mg in the Phase 3 trials: pre- and post-retraining



Treated set of patients

Subgroup analyses of adjudicated DKA with empagliflozin 10 mg and 25 mg

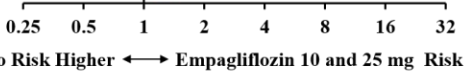
Due to the low number of DKA events, subgroup analyses were not feasible for the 2.5 mg dose (as discussed in Section 3.1). Subgroup analyses by baseline characteristics were however performed for the empagliflozin 10 and 25 mg doses. The aim was to better understand whether any baseline characteristics could potentially be associated with a higher risk of DKA. The rate of 'certain or potential' DKA by subgroups is presented for the combined treatment groups of empagliflozin 10 mg and 25 mg in Figure 32.

Baseline characteristics found to be associated with a higher rate of 'certain or potential' DKA in all treatment groups, including placebo, were 'insulin pump use' and 'previous history of DKA'.

The DKA risk was consistently elevated with empagliflozin 10 and 25 mg versus placebo across all subgroups, with the highest increase versus placebo observed in female patients.

Figure 32 Certain and potential DKA by subgroup for the combined treatment groups of empagliflozin 10 mg and 25 mg in the Phase 3 trials

Treatment Comparison	Empa 10 and 25 mg Pooled n/N	Placebo n/N	Hazard Ratio (95% CI)	p-value for interaction
Sex				
Male	12/471	7/226	0.80 (0.31, 2.03)	0.0034
Female	49/509	4/258	6.28 (2.27, 17.41)	
Insulin Dose				
<0.7	41/512	6/253	3.44 (1.46, 8.11)	0.3631
≥0.7	19/399	5/202	1.88 (0.70, 5.03)	
Insulin Therapy				
MDI	20/617	4/305	2.47 (0.84, 7.23)	0.8453
CSII	41/363	7/179	2.82 (1.27, 6.29)	
BMI				
≤27 kg/m²	27/395	8/216	1.91 (0.87, 4.19)	0.1816
>27 kg/m²	34/585	3/268	5.02 (1.54, 16.34)	
Region				
US	19/222	5/121	1.90 (0.71, 5.08)	0.3786
Non-US	42/758	6/363	3.41 (1.45, 8.03)	
History of DKA[2]				
0 events	52/884	8/416	3.05 (1.45, 6.42)	0.6186
≥1 events	9/91	3/66	2.08 (0.56, 7.69)	
Baseline HbA_{1c}				
<8.0%	31/423	4/209	3.87 (1.37, 10.97)	0.3541
≥8.0%	30/557	7/275	2.07 (0.91, 4.71)	
eGFR				
<60	2/43	0/14	N/A	
60 to <90	19/232	3/109	2.93 (0.87, 9.9)	0.8789
≥90	35/654	7/341	2.61 (1.16, 5.89)	
Age				
<30	15/178	4/96	1.94 (0.64, 5.84)	0.5980
30 to <45	15/289	2/164	4.23 (0.97, 18.51)	
45 to <65	24/444	3/198	3.65 (1.1, 12.11)	
≥65	7/69	2/26	1.22 (0.25, 5.87)	



Placebo Risk Higher ⟷ Empagliflozin 10 and 25 mg Risk Higher

8.7.2.4.2 Ketone-related events

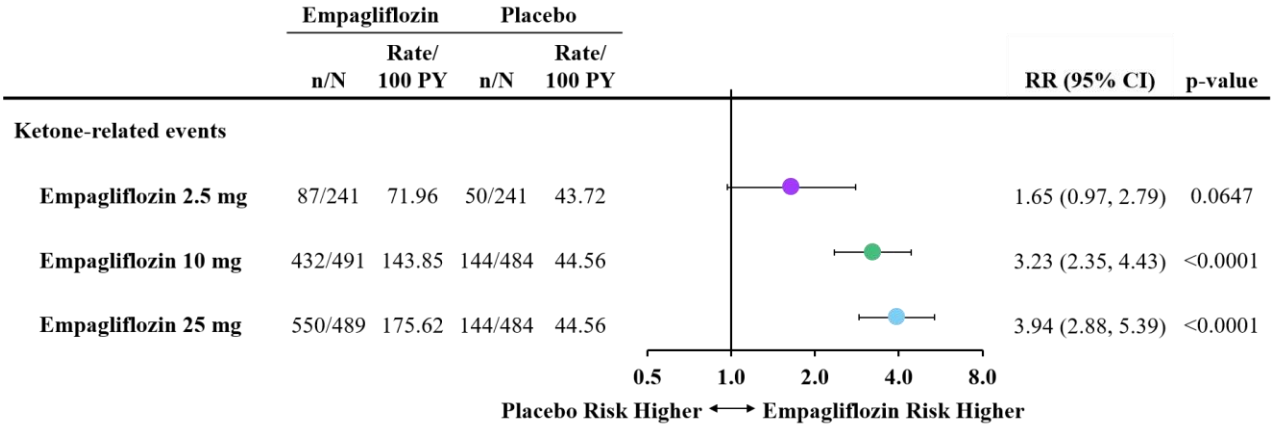
Ketone-related events, were defined as the occurrence of any of the following events:

1. Adjudicated certain or potential DKA
2. Adjudicated ketosis
3. Ketone values >1.5 mmol/L, even if not qualifying as triggers for adjudication

An increased rate of ketone-related events, mainly consisting of episodes of ketosis without acidosis, was observed in all empagliflozin groups versus placebo.

Relative to placebo, this increase was lower with the 2.5 mg dose as compared with the higher doses (Figure 33).

Figure 33 Patients with ketone-related events in EASE-2 and EASE-3



8.7.2.5 Genital infections and urinary tract infections

Genital infections

Genital infection is a known risk with SGLT2 inhibitors. In the EASE program, genital infections were more frequent in the empagliflozin treatment groups than in the placebo group. The increase relative to placebo was lower with the 2.5 mg dose than with the higher doses:

- EASE-3: placebo: 2.5%, empagliflozin 2.5 mg: 4.1%
- Pooled Phase 3 trials: placebo: 3.3%, empagliflozin 10 mg: 11.2%, empagliflozin 25 mg: 11.5%

There were no serious genital infections reported for empagliflozin 2.5 mg.

Three patients had an event categorized as severe on the two higher doses (empagliflozin 10 mg: 1 patient, empagliflozin 25 mg: 2 patients). Eleven patients had an event that led to treatment discontinuation; all except one patient were in the empagliflozin 10 mg and 25 mg groups. The majority of patients with genital infections had 1 episode.

The majority of patients with genital infections were female. Genital infections were more frequently reported in patients with a history of genital infection and those with a history of urinary tract infections. The pooled dataset (empagliflozin 10 mg and 25 mg) showed a trend towards more genital infections in patients ≥65 years.

Urinary tract infections

The frequencies of patients with urinary tract infections were similar across the treatment groups in EASE-3 that included 2.5 mg and in the pooled analysis of EASE-2 and EASE-3 (empagliflozin 10 mg and 25 mg). None of the urinary tract infections was severe and few led to treatment discontinuation.

The frequency of patients with urinary tract infections was higher if there was a history of urinary tract infections or a history of genital infections compared with patients without such histories. There was also a trend for higher frequencies for urinary tract infections in the empagliflozin treatment groups compared with placebo in patients with these medical histories.

9. References

1. Atkinson, M.A., G.S. Eisenbarth, and A.W. Michels, *Type 1 diabetes.* Lancet, 2014. **383**(9911): p. 69-82.
2. Bullard, K.M., et al., *Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016.* MMWR Morb Mortal Wkly Rep, 2018. **67**(12): p. 359-361.
3. Cho, N.H., et al., *IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045.* Diabetes Res Clin Pract, 2018. **138**: p. 271-281.
4. Livingstone, S.J., et al., *Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010.* JAMA, 2015. **313**(1): p. 37-44.
5. McKnight, J.A., et al., *Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison.* Diabet Med, 2015. **32**(8): p. 1036-50.
6. Nathan, D.M., et al., *Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions.* Diabetes, 2013. **62**(12): p. 3976-86.
7. Nathan, D.M., et al., *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.* N Engl J Med, 1993. **329**(14): p. 977-86.
8. Subramanian, S. and I.B. Hirsch, *Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes Mellitus: Implications of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study 30-Year Follow-up.* Endocrinol Metab Clin North Am, 2018. **47**(1): p. 65-79.
9. *Glycemic Targets: Standards of Medical Care in Diabetes.* Diabetes Care, 2018. **41**(Suppl 1): p. S55-s64.
10. Miller, K.M., et al., *Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange clinic registry.* Diabetes Care, 2015. **38**(6): p. 971-8.
11. Lachin, J.M., et al., *Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC.* Diabetes, 2015. **64**(2): p. 631-42.
12. Weinstock, R.S., et al., *Type 1 diabetes in older adults: Comparing treatments and chronic complications in the United States T1D Exchange and the German/Austrian DPV registries.* Diabetes Res Clin Pract, 2016. **122**: p. 28-37.
13. Ryan, G.J., L.J. Jobe, and R. Martin, *Pramlintide in the treatment of type 1 and type 2 diabetes mellitus.* Clin Ther, 2005. **27**(10): p. 1500-12.
14. Lu, J., et al., *Effects of sodium-glucose cotransporter (SGLT) inhibitors in addition to insulin therapy on glucose control and safety outcomes in adults with type 1 diabetes: A meta-analysis of randomized controlled trials.* Diabetes Metab Res Rev, 2019: p. e3169.
15. Taylor, S.I., J.E. Blau, and K.I. Rother, *SGLT2 Inhibitors May Predispose to Ketoacidosis.* J Clin Endocrinol Metab, 2015. **100**(8): p. 2849-52.
16. Ferrannini, E., et al., *Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients.* J Clin Invest, 2014. **124**(2): p. 499-508.

17. Goldenberg, R.M., et al., *Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: The STOP DKA Protocol.* Diabetes Obes Metab, 2019. **21**(10): p. 2192-2202.
18. Yu, X., S. Zhang, and L. Zhang, *Newer Perspectives of Mechanisms for Euglycemic Diabetic Ketoacidosis.* Int J Endocrinol, 2018. **2018**: p. 7074868.
19. *FDA Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.* 2008.
20. Fahrmann, E.R., et al., *Severe hypoglycemia and coronary artery calcification during the diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study.* Diabetes Res Clin Pract, 2015. **107**(2): p. 280-9.
21. Jacobson, A.M., et al., *Long-term effect of diabetes and its treatment on cognitive function.* N Engl J Med, 2007. **356**(18): p. 1842-52.
22. Pettus, J.H., et al., *Incidences of Severe Hypoglycemia and Diabetic Ketoacidosis and Prevalence of Microvascular Complications Stratified by Age and Glycemic Control in U.S. Adult Patients With Type 1 Diabetes: A Real-World Study.* Diabetes Care, 2019.
23. Weinstock, R.S., et al., *Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry.* J Clin Endocrinol Metab, 2013. **98**(8): p. 3411-9.
24. *FDA Public Workshop: Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c).* https://www.fda.gov/drugs/news-events-human-drugs/public-workshop-diabetes-outcome-measures-beyond-hemoglobin-a1c-hba1c. 2016.
25. *Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2017. **40**(1): p. 155-157.
26. Home, P.D., A. Lindholm, and A. Riis, *Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial.* Diabet Med, 2000. **17**(11): p. 762-70.
27. Witthaus, E., J. Stewart, and C. Bradley, *Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes.* Diabet Med, 2001. **18**(8): p. 619-25.
28. *Food and Drug Administration Moderization Act.* 1997.
29. Mehrotra, N., et al., *The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy.* Int J Impot Res, 2007. **19**(3): p. 253-64.
30. Perkins, B.A., et al., *Exploring Patient Preferences for Adjunct-to-Insulin Therapy in Type 1 Diabetes.* Diabetes Care, 2019. **42**(9): p. 1716-1723.
31. *FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.* 1998.
32. Arora, S., et al., *Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: {beta}-hydroxybutyrate versus the urine dipstick.* Diabetes Care, 2011. **34**(4): p. 852-4.