

Empagliflozin as Adjunct to Insulin in Patients with Type 1 Diabetes Mellitus: Modelling Rate and Severity of Hypoglycemic Events

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BACKGROUND

- Empagliflozin is a potent and selective sodium glucose cotransporter 2 inhibitor. As its mechanism of action is insulin-independent, empagliflozin is under clinical investigation as adjunct to insulin to improve glycemic control in patients with type 1 diabetes mellitus (T1DM).
- A Phase IIa, 4-week, randomized, double-blind, placebo-controlled trial (EASE-1) of empagliflozin as adjunct to insulin in patients with T1DM reported that rates of symptomatic hypoglycemia with plasma glucose <54 mg/dL were generally lower with empagliflozin than with placebo.¹

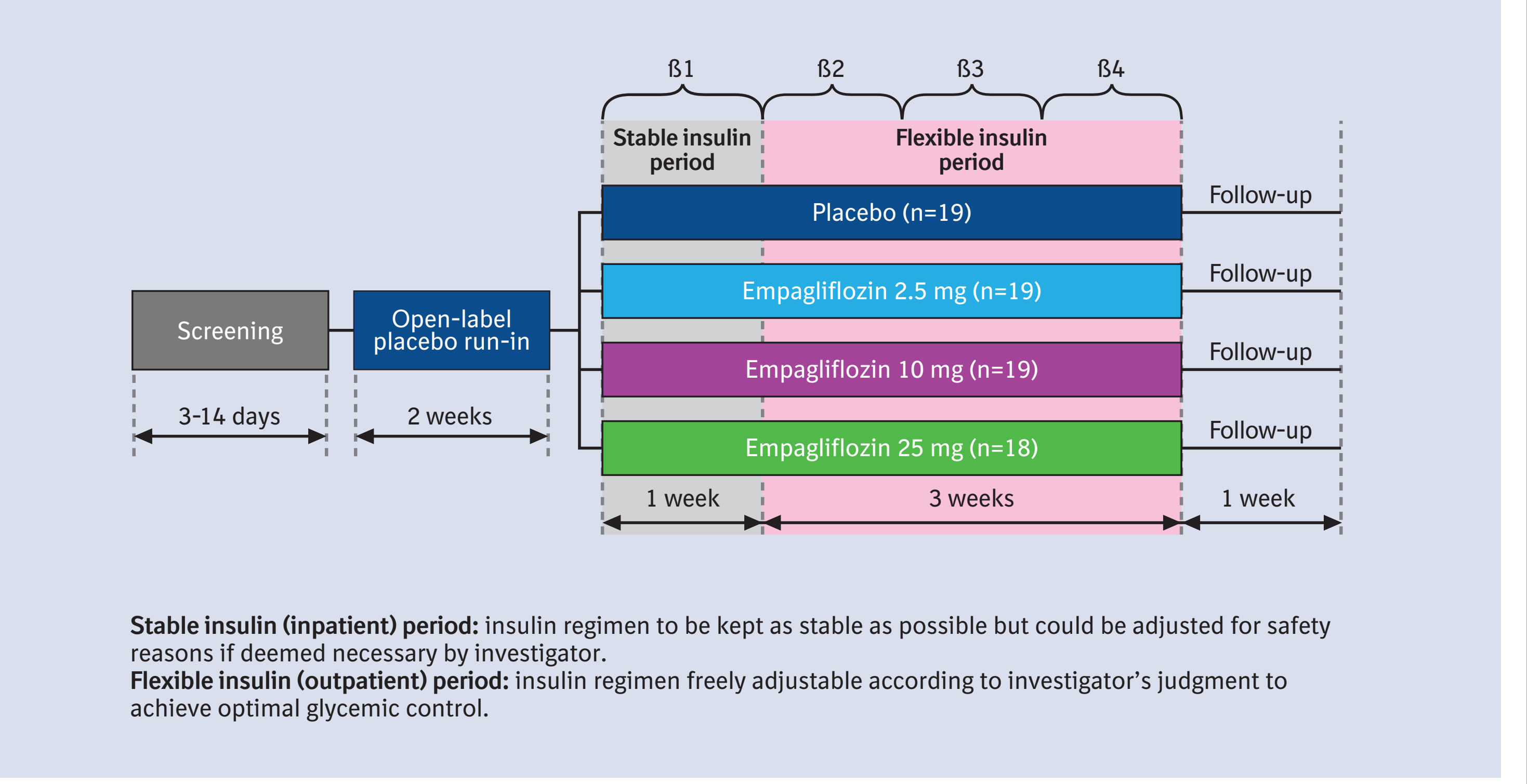
OBJECTIVE

- To develop a repeated time to categorical event (RTTCE) model in order to describe the rate and severity of hypoglycemia and investigate factors influencing both parameters in an exploratory analysis.

METHODS

- The study design of the EASE-1 trial can be seen in **Figure 1**.
- Hypoglycemic event data from the EASE-1 trial were analyzed. Hypoglycemic events were classified as:
 - Grade 1: Asymptomatic hypoglycemia with plasma glucose ≤70 mg/dL
 - Grade 2: Symptomatic hypoglycemia with plasma glucose ≥54 to ≤70 mg/dL and no assistance required
 - Grade 3: Symptomatic hypoglycemia with plasma glucose <54 mg/dL and no assistance required
 - Grade 4: Hypoglycemia requiring assistance.
- To describe the repeated time to events (RTTE), a parametric survival model was fitted to the data using NONMEM 7.3. To simultaneously capture the severity of events, the RTTE model (**Equations 1 and 2**) was combined with an ordered categorical model (**Equation 3**) to form the RTTCE model.² The performance of the model was evaluated with visual predictive checks of the Kaplan-Meier curves (**Figure 2**). The influence of study- and patient-related covariates were explored and visualized in a forest plot (**Figure 3**).
 - The final model estimates were employed to perform 1000 simulations of a 60-day placebo-controlled trial with 200 patients per arm for empagliflozin 2.5, 10 and 25 mg. Simulations took into account between-subject variability, but not parameter uncertainty (assuming the estimated parameters to be true). Simulated trials represented the expected results once insulin titration was stable, and hence: individual patient records were resampled from the original dataset (fourth week of original study) in order to preserve the covariance between the covariates
 - The shape parameter (β) was fixed to the estimated value during the fourth week of the EASE-1 trial (β=β₄).

Figure 1. Study design (EASE-1)¹



RESULTS

- The analysis dataset comprised 75 patients (53 male = 70.7%) with a median (2.5th – 95th percentile) age of 43.0 (21.7 – 61.0) years, weight of 78.6 (52.2 – 105) kg, eGFR of 102 (78.7 – 128) mL/min/1.73m² and a baseline HbA1c of 8.20 (7.19 – 9.61)%.
- Observed rates of grade 2 and 3 hypoglycemic events for patients on active treatment were lower during the flexible insulin period compared with rates during the stable insulin period. There were higher rates of grade 2 and 3 hypoglycemic events during the stable insulin period for empagliflozin 10 and 25 mg (not 2.5 mg) compared to placebo, and lower rates during the flexible insulin period for all treatment groups compared to placebo, which was more pronounced for the grade 3 hypoglycemic events. There was only one grade 4 hypoglycemic event recorded (placebo group), which was pooled with the grade 3 events during the analysis.
- Reporting-rates of asymptomatic and symptomatic hypoglycemia proved to have a different profile and thus, asymptomatic hypoglycemia were excluded from the analysis. The rate of symptomatic hypoglycemia was best described by a Gompertz model (**Equation 1**).

Equation 1. Hazard model equation

$$h(t) = Base \cdot e^{(\beta \cdot (t-t_p))} \cdot e^{(CoefG \cdot (CGM - 150) + CoefE1 \cdot AUC_{SS} + \frac{Emax \cdot AUC_{SS}}{AUC_{50} + AUC_{SS}} + CoefS \cdot sex)}$$

Base: base hazard; β: shape parameter; t: time in hours; t_p: time of previous event in hours; CoefG: coefficient describing the influence of mean glucose concentration from the continuous glucose monitoring system on hazard; CGM: mean glucose concentration from the continuous glucose monitoring system in mg/dL; CoefE1: coefficient describing the influence of empagliflozin AUC_{ss} on hazard during the first study day; E_{max}: maximum effect of empagliflozin AUC_{ss} on hazard; AUC₅₀: AUC_{ss} necessary to achieve 50% of the E_{max}; CoefS: coefficient describing the influence of sex (0 = male, 1 = female) on hazard once insulin was being titrated (weeks 2–4).

Equation 2. Evolution of β parameter over time

β ₁ = β ₀ - (t*k1)	During stable insulin period	→ β = β ₁
β ₂ = β ₀ - (168*k1)	During first flexible insulin period	→ β = β ₂
β ₃ = β ₂ - (k2*(t-336))	During second flexible insulin period	→ β = β ₃
β ₄ = β ₂ - (k2*(504-336))	Once insulin titration was stabilized	→ β = β ₄

Equation 3. Ordered categorical model

Logits for probability of Y ≥3	LGE3 = B1 + ETA(2); (B1: cut point defining grade 3)
Probabilities for Y ≥3	PGE3 = EXP(LGE3)/(1 + EXP(LGE3))
Probability of event being grade 2	P2 = (1 - PGE3)
Probability of event being grade ≥3	P3 = (PGE3)

Figure 2. Visual predictive check of Kaplan-Meier curves stratified by severity of hypoglycemia for the first 3 events in each severity level

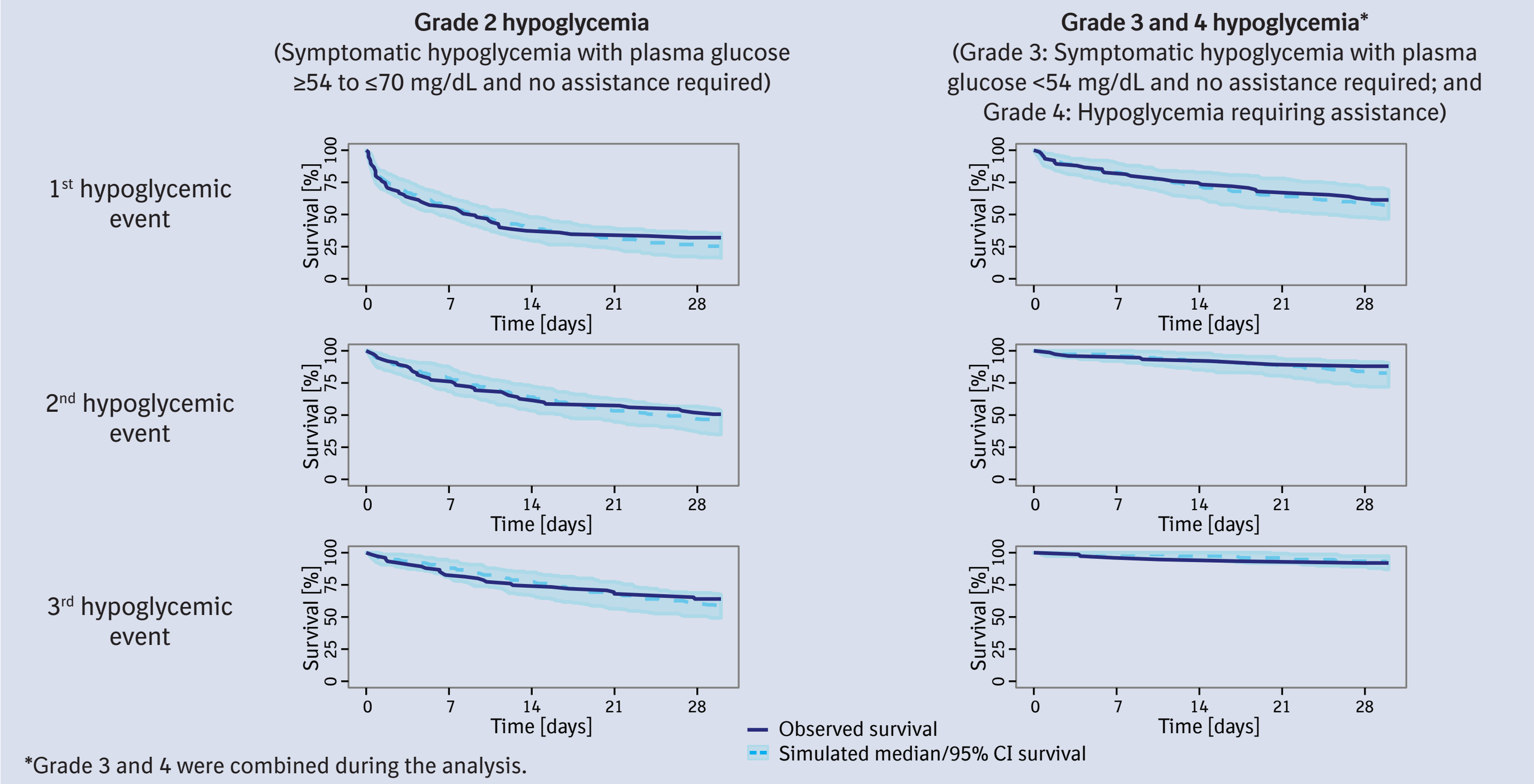
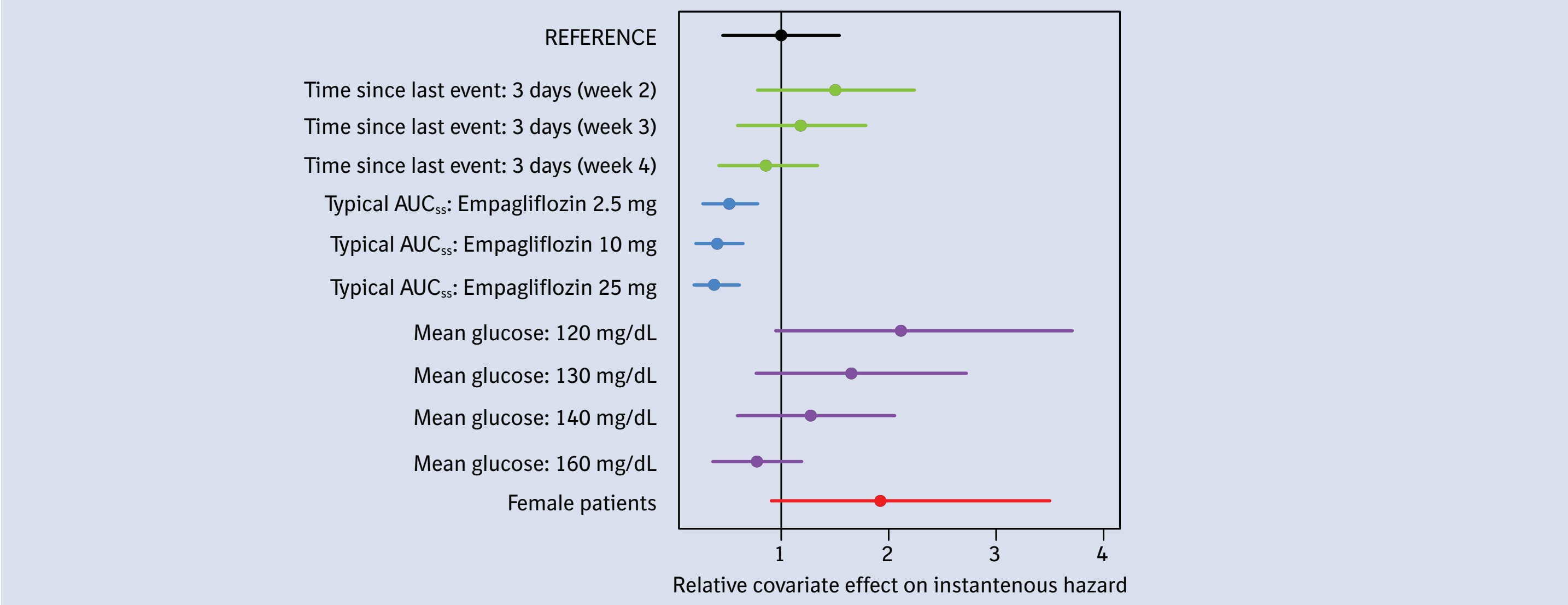


Figure 3. Relative covariate effects on instantaneous hazard of having a hypoglycemic event



Reference: male patient in placebo group, 0 hours after last hypoglycemic event, with mean glucose concentration since last event of 150 mg/dL. Solid point represents the median and horizontal lines represent the 95% CIs for each covariate effect. CIs were determined based on n=1000 simulations from the variance-covariance matrix of the final model. Covariate effects for continuous covariates (time since last event, empagliflozin AUC_{ss}, mean glucose since last event) were evaluated at fixed values to represent the observed range for each variable.

- Figure 3** shows the evolution of the shape factor (β) over the trial (reflected as time since last event in the respective study week) as well as relative covariate effects on instantaneous hazard of having a hypoglycemic event:
 - β proved to be influenced by insulin titration: during the stable insulin period, instantaneous hazard increased over time (β>0), but once insulin was flexible and patients were stabilized, instantaneous hazard decreased over time (β<0)
 - Higher empagliflozin AUC_{ss} were related to a lower risk of hypoglycemia
 - Low mean glucose concentrations and female sex were related to a higher risk of hypoglycemia.
- The simultaneous description of rate and severity of events allowed identification of an inverse correlation between them.
- Simulation results:
 - Patients receiving empagliflozin 2.5, 10 and 25 mg experienced 31 (51 to 3)%¹, 61 (72 to 45)%² and 48 (63 to 24)%³ less grade 2 hypoglycemic events per patient versus placebo
 - Similarly, patients receiving empagliflozin 2.5, 10 and 25 mg experienced 32 (52 to 6)%¹, 63 (74 to 48)%² and 50 (65 to 28)%³ less grade 3 hypoglycemic events per patient versus placebo
 - A lower number of counts is expected in patients treated with empagliflozin versus placebo, especially in those receiving empagliflozin 10 or 25 mg
 - Differences in simulation outcomes between dose groups are due to interplay of the effect of empagliflozin AUC_{ss} and inversely correlated mean glucose concentrations on the hazard.

Table 1. Final model parameter estimates and 95% CIs resulting from a non-parametric bootstrap (n=1000)

Parameter	Estimate	95% CI	Parameter	Estimate	95% CI
BASE	0.00566	0.00262, 0.00903	E _{max}	-0.992	-1.70, -0.262
BETA0	0.0688	0.0524, 0.102	AUC ₅₀	267	267, 267
K1	0.000375	0.000282, 0.000565	COEFSEX	0.674	0.045, 1.41
K2	0.0000469	0.0000364, 0.0000634	ω ² _{BASE}	0.498	0.197, 0.991
B1	-1.34	-2.07, -0.883	ω ² _{BASE} ω ² _{B1}	-0.677	-1.19, -0.152
COEFG	-0.0256	-0.0342, -0.0169	ω ² _{B1}	1.69	0.631, 3.85
COEFEMPAD1	0.000500	0.000259, 0.000741	ω ² _{COEFG}	0.000238	0.0000259, 0.000535

DISCUSSION

- During model development, asymptomatic events were excluded due to their lower clinical relevance and to avoid model misspecifications because different reporting patterns for symptomatic versus asymptomatic events were observed (asymptomatic events only being detected at scheduled glucose measurements; symptomatic events implied additional glucose measurements).
- Patients with lower mean glucose levels from the subcutaneous continuous monitoring system had a higher risk of hypoglycemia, probably due to the proximity of blood glucose levels to the hypoglycemia threshold.
- Gender as a covariate might be explained by the finding that estrogen appears to play a major role in the sexual dimorphism present in counter-regulatory responses to hypoglycemia in healthy humans.³

CONCLUSIONS

- The proposed model described symptomatic hypoglycemia reported in the trial and provided information regarding patient- and study-specific factors influencing the risk of having a hypoglycemic event.
- This work represents a first exploratory step in the direction of a model-informed exposure-risk-benefit evaluation for empagliflozin as a treatment option for patients with T1DM, and will be refined as further data become available.

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REFERENCES

1. Pieber TR et al. *Diabetes Obes Metab* 2015;17(10):928-35. 2. Plan EL et al. *Clin Pharmacol Ther* 2010;88(2):255-9. 3. Sandoval DA et al. *Diabetes* 2003;52(7):1749-55.