Safety, Tolerability, Pharmacokinetics,and Pharmacodynamics of Multiple Rising Doses of Empagliflozin in Patients with Type 2 Diabetes Mellitus

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Sara Al-Sharhan, Pharm D intern- KSU

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ORIGINAL RESEARCH

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Rising Doses of Empagliflozin in Patients with Type 2 Diabetes Mellitus

Tim Heise · Leo Seman · Sreeraj Macha · Peter Jones · Alexandra Marquart · Sabine Pinnetti · Hans J. Woerle · Klaus Dugi

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Outline

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- Introduction
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Background

Definition of diabetes mellitus:

- Diabetes is a chronic condition caused by an absolute lack of insulin or relative lack of insulin as a result of impaired insulin secretion and action.
- Clinical characteristics are symptomatic glucose intolerance resulting in hyperglycemia and alterations in lipid and protein metabolism.

Background

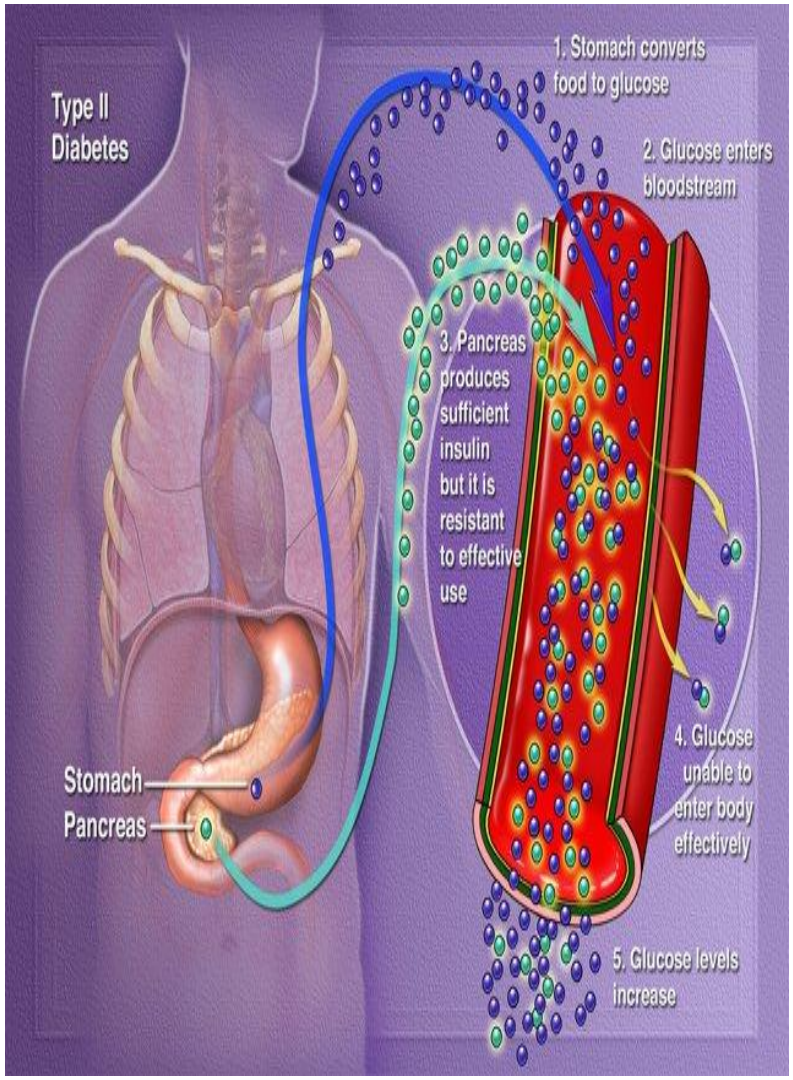
Types of diabetes mellitus:

- Type 1 diabetes mellitus- 5-10 % of diabetic population.
- Type 2 diabetes mellitus- 90 % of diabetic population.
- Gestational diabetes mellitus (GDM).

Background

Definition of Type2 diabetes mellitus(T2DM):

- Diabetes mellitus of a common form that develops especially in adults and most often in obese individuals and that is characterized by hyperglycemia resulting from impaired insulin utilization coupled with the body's inability to compensate with increased insulin production.

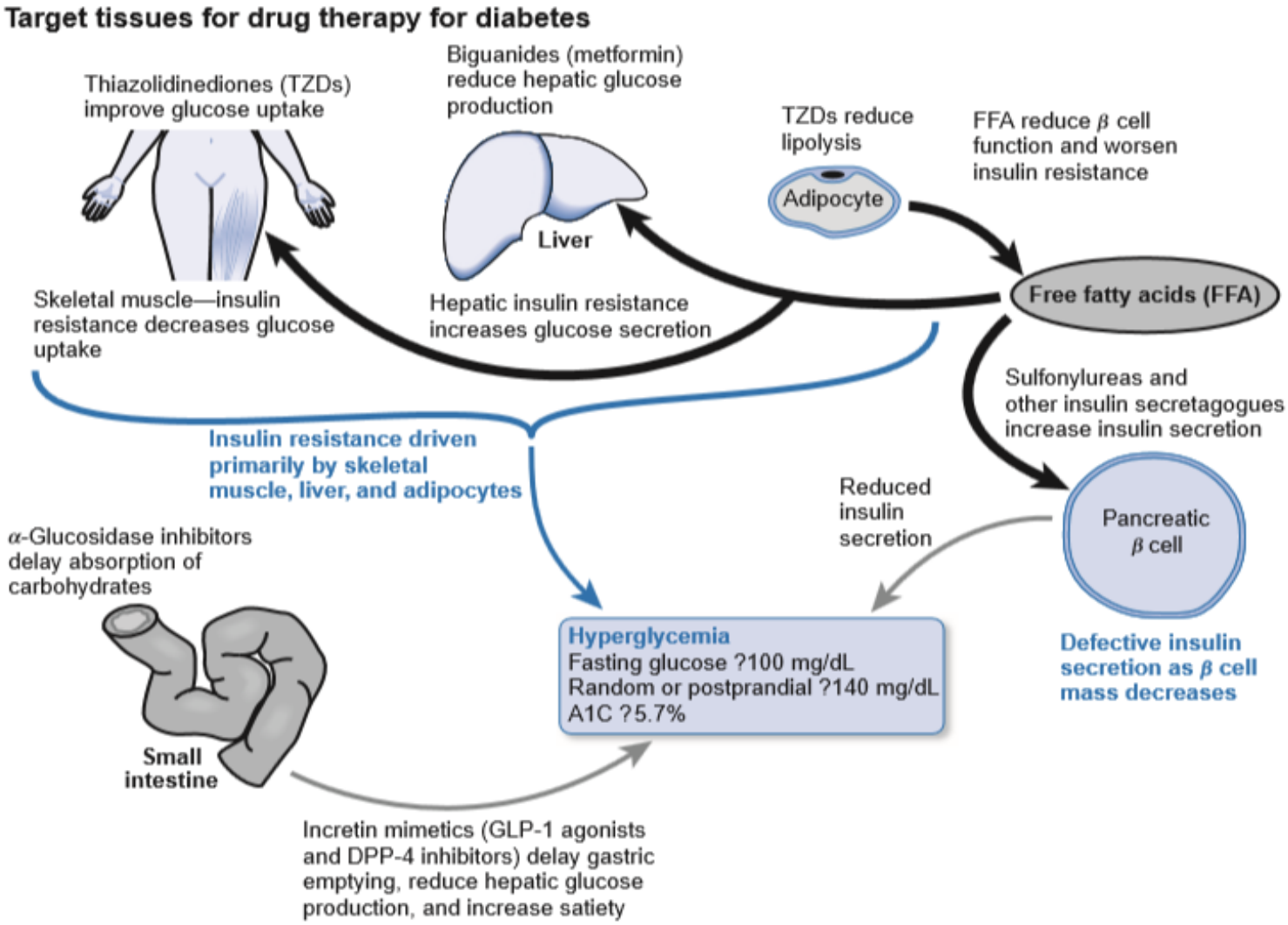


Background

Treatment of T2DM:

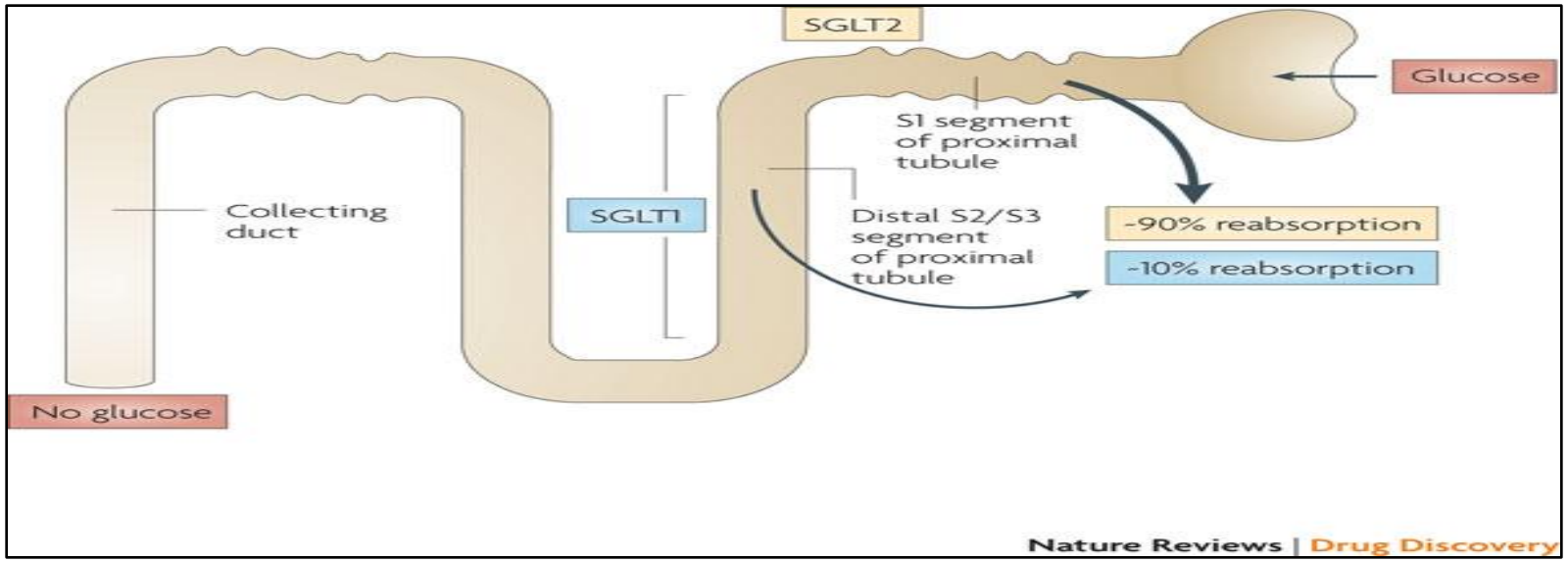
- The treatment of T2DM have focused on improving insulin secretion and insulin sensitivity with the aim of lowering blood glucose levels to meet glycosylated hemoglobin (HbA1c) targets while avoiding hypoglycemia.

Background


Target tissues for drug therapy for diabetes
Thiazolidinediones (TZDs) improve glucose uptake
Biguanides (metformin) reduce hepatic glucose production
TZDs reduce lipolysis
FFA reduce β cell function and worsen insulin resistance
Adipocyte
Liver
Skeletal muscle—insulin resistance decreases glucose uptake
Hepatic insulin resistance increases glucose secretion
Free fatty acids (FFA)
Sulfonylureas and other insulin secretagogues increase insulin secretion
Insulin resistance driven primarily by skeletal muscle, liver, and adipocytes
Reduced insulin secretion
Pancreatic β cell
α-Glucosidase inhibitors delay absorption of carbohydrates
Hyperglycemia
Fasting glucose ?100 mg/dL
Random or postprandial ?140 mg/dL
A1C ?5.7%
Defective insulin secretion as β cell mass decreases
Small intestine
Incretin mimetics (GLP-1 agonists and DPP-4 inhibitors) delay gastric emptying, reduce hepatic glucose production, and increase satiety

Introduction

- Sodium glucose cotransporter 2 (SGLT2) inhibitors offer an alternative mechanism for control of hyperglycemia in T2DM.
- They reduce glucose reabsorption in the kidney and thereby increasing urinary glucose excretion (UGE).



Introduction

- Empagliflozin is an SGLT2 inhibitor in development as a treatment for T2DM.
- In in vitro studies, empagliflozin exhibited highly potent inhibition of SGLT2.

Outcome

- Primary outcome: safety and tolerability.

- Secondary outcome: Pharmacokinetic and pharmacodynamic parameters.

PICO OF THE STUDY

P	• Adult patients with T2DM
I	• Empagliflozin (2.5, 10, 25, and 100 mg)
C	• Placebo
O	• Safety and tolerability

P: Population, I: Intervention, C: Comparison, O: Outcome.

Clinical question

- In adult patients with T2DM, Are rising doses of empagliflozin well tolerated and safe in compared to placebo to produce blood glucose lowering effects?

METHOD-INTERNAL VALIDITY

- patients with T2DM treated with diet and exercise only.
- Taking ≤2 oral anti-diabetic agents with at least one agent taken at ≤50% of its maximum dose.
- HbA1c ≤8.5% at screening.
- Body mass index 18.5–40 kg/m2.

Inclusion criteria

Exclusion criteria

- Patients on insulin or thiazolidinediones.
- Fasting blood glucose >240mg/dL.
- Postprandial blood glucose >400 mg/dL
- Clinically significant concomitant diseases
- Abnormalities in the screening laboratory.

Method-Internal validity

Randomization:

- Patients were randomized upon admission to the trial center to one of four doses of empagliflozin (2.5, 10, 25, and 100 mg).
- Treatment allocation was carried out according to a randomized list of patient and medication numbers.
- Within each dose group, patients were randomized to receive placebo or active drug.

Method-Internal validity

Blindness:

- patients and investigators were double blinded until the study had completed.

METHOD-INTERNAL VALIDITY

Similarity of the groups:

Table 1 Baseline characteristics

	Placebo	Empagliflozin 2.5 mg qd	Empagliflozin 10 mg qd	Empagliflozin 25 mg qd	Empagliflozin 100 mg qd	Total
Patients, *N* (%)	12 (100.0)	9 (100.0)	9 (100.0)	9 (100.0)	9 (100.0)	48 (100.0)
Gender, *N* (%)						
Male	10 (83.3)	7 (77.8)	8 (88.9)	7 (77.8)	7 (77.8)	39 (81.3)
Female	2 (16.7)	2 (22.2)	1 (11.1)	2 (22.2)	2 (22.2)	9 (18.8)
Ethnicity, *N* (%)						
White	12 (100.0)	9 (100.0)	9 (100.0)	9 (100.0)	8 (88.9)	47 (97.9)
Black	0	0	0	0	1 (11.1)	1 (2.1)
Age, years, median (range)	59.0 (51–67)	57.0 (37–67)	57.0 (33–66)	58.0 (40–68)	61.0 (50–68)	57.5 (33–68)
Weight, kg, median (range)	100.6 (69.5–118.4)	100.1 (84.2–112.9)	101.7 (71.5–122.8)	91.1 (67.2–121.4)	85.4 (71.2–100.1)	94.3 (67.2–122.8)
BMI, kg/m^2, median (range)	32.9 (24.3–38.7)	31.9 (28.8–34.3)	30.3 (25.3–39.2)	31.5 (26.3–36.3)	27.6 (23.9–32.0)	31.1 (23.9–39.2)
Duration of diabetes, years, mean (SD)	4.7 (2.4)	5.5 (3.9)	4.9 (2.9)	7.6 (5.1)	9.2 (6.8)	6.3 (4.5)
Fasting plasma glucose, mg/dL, mean (SD)	156.9 (24.1)	144.1 (38.7)	150.1 (32.1)	142.2 (24.3)	164.3 (26.6)	151.9 (29.2)
Creatinine clearance, mL/min, mean (SD)	103.8 (25.6)	125.3 (38.3)	78.0 (24.3)	146.8 (20.6)	117.2 (20.2)	113.6 (33.9)
Any concomitant diagnosis, *N* (%)	9 (75.0)	5 (55.6)	6 (66.7)	5 (55.6)	7 (77.8)	32 (66.7)
Hypertension	7 (58.3)	3 (33.3)	4 (44.4)	4 (44.4)	5 (55.6)	23 (47.9)
Hypercholesterolemia	1 (8.3)	2 (22.2)	1 (11.1)	0	3 (33.3)	7 (14.6)
Any concomitant anti-diabetic medication,[a] *N* (%)	11 (91.7)	8 (88.9)	9 (100.0)	8 (88.9)	7 (77.8)	43 (89.6)
Metformin	8 (66.7)	7 (77.8)	8 (88.9)	8 (88.9)	5 (55.6)	36 (75.0)
Other	3 (25.0)	1 (11.1)	1 (11.1)	0 (0.0)	3 (33.3)	7 (14.6)

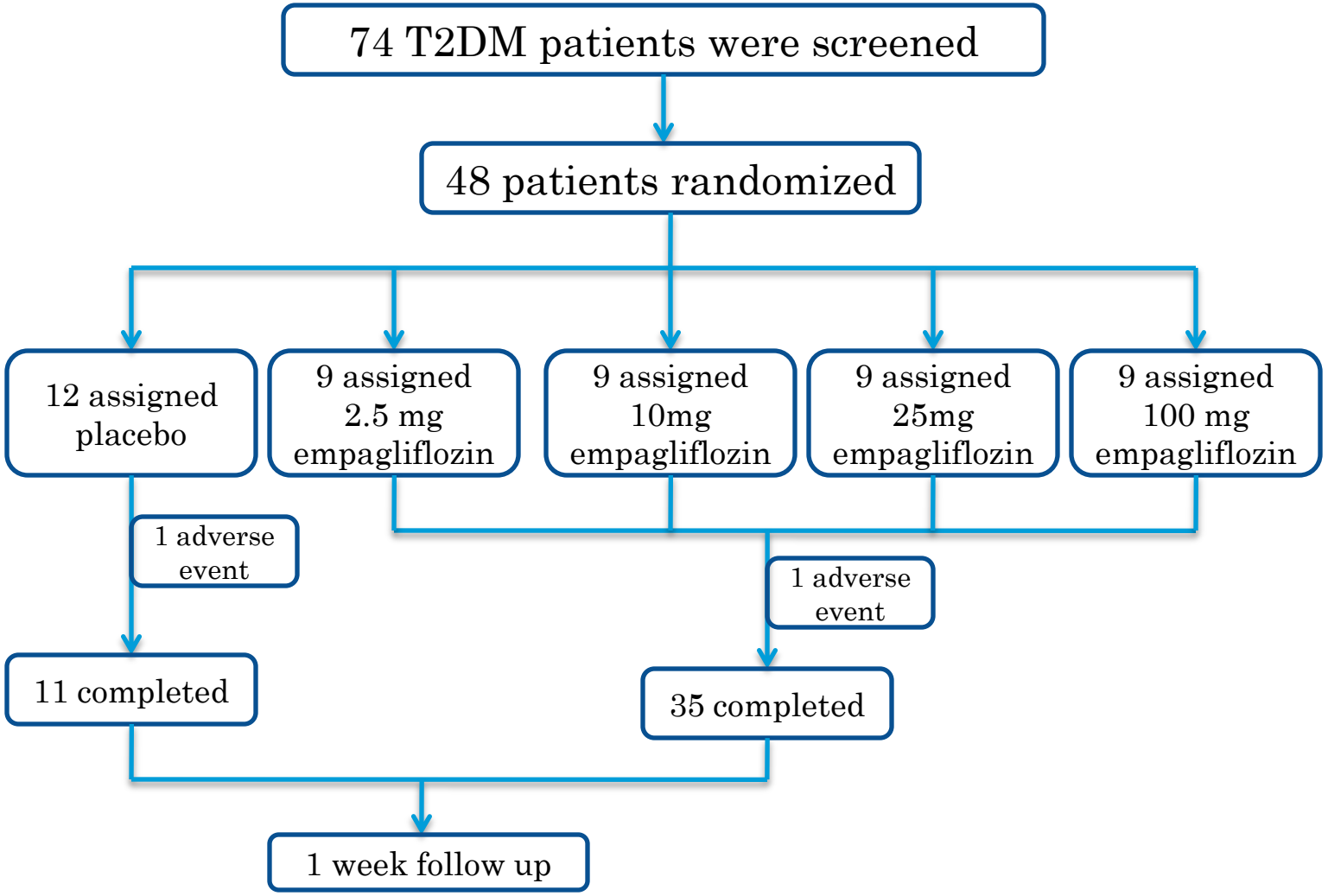
Method-Internal validity

Similarity in co-intervention of the groups:

- Patients received a single dose on day 1 and once-daily dosing on days 3–9.
- The dosing on day 2 was skipped to allow estimation of the terminal elimination half-life after a single dose to compare with the steady state half-life.
- Study drug was administered at the same time every day with 240mL of water.
- Patients were fasted overnight for 10 h on days -2, -1, 1, 8, and 9.
- An end-of-study examination was carried out in the 1-week post-treatment period (days 15–21).
- An oral glucose tolerance test (OGTT; administration of 75 g glucose solution after overnight fasting) was performed on days -1, 1,and 9.

METHOD-INTERNAL VALIDITY

Maintenance for adequate follow up:



RESULTS

Table 2 Summary of adverse events occurring in more than 5% of the treated set, *n* (%)

	Placebo $N = 12$	Empagliflozin 2.5 mg qd $N = 9$	Empagliflozin 10 mg qd $N = 9$	Empagliflozin 25 mg qd $N = 9$	Empagliflozin 100 mg qd $N = 9$
Patients with any AE	5 (41.7)	6 (66.7)	5 (55.6)	5 (55.6)	3 (33.3)
Headache	1 (8.3)	0	1 (11.1)	2 (22.2)	0
Diarrhea	1 (8.3)	2 (22.2)	0	0	0
Pruritus	1 (8.3)	1 (11.1)	0	1 (11.1)	0
Hypoglycemia	0	0	2 (22.2)	1 (11.1)	0

Data from the treated set ($n = 48$)
AE adverse event

Results

	No. of patients	Positive outcome	Negative outcome
Intervention	36	19	17
Control	12	5	7

- Control event rate(CER)= 42%
- Experimental event rate(EER)= 53%
- Absolute risk reduction= CER-EER= 11%
- No. needed to treat (NNT)= 1/ARR= 9

We need to treat 9 patients with empagliflozin for T2DM to prevent 1 patient from experiencing adverse events.

Results

Table 3 Mean (SD) weighted MDG at baseline and after administration of oral empagliflozin doses (2.5–100 mg) without an oral glucose tolerance test

Empagliflozin dose	Number of patients	Mean MDG (SD) mg/dL			
		Baseline (day −2)	Day 8	Mean (least squares) change from baseline to day 8	Difference to placebo
Placebo	12[a]	169 (30.5)	153 (24.5)	−13.5	
2.5 mg qd	9	161 (57.3)	134 (42.7)	−29.0	−15.5, $p < 0.05$
10 mg qd	9[b]	160 (35.8)	124 (18.9)	−37.0	−23.5, $p < 0.01$
25 mg qd	9	159 (32.8)	133 (36.2)	−28.5	−15.0, $p = 0.052$
100 mg qd	9	185 (33.0)	154 (17.9)	−24.1	−10.6, $p = 0.168$

Data from the treated analysis set ($n = 48$). Weighted MDG, weighted mean daily glucose estimated by dividing the area under the 24-h glucose curve by 24 h for each patient on each day

SD standard deviation

[a] $n = 11$ on day 8

[b] $n = 8$ on day 8

Discussion

Limitation:

- Short term study.
- Small sample size.
- Control and treatment groups were not similar.
- The method of blindness was not mentioned.
- The method of randomization.

Conclusion

- Empagliflozin (2.5–100 mg) resulted in significant and clinically meaningful blood glucose lowering effects.

- Analysis of safety data showed that empagliflozin was well tolerated in patients with T2DM.

Conclusion

- Marketing authorization application (MAA) for empagliflozin has been accepted for review by the European Medicines Agency (EMA).

Recommendations

- More long-term studies in patients with T2DM will provide more information on the safety and tolerability of empagliflozin.

Thank you..