SUPPLEMENTARY DATA

Supplementary Table 1. Differences in DKA Adjudication Definition (note: the are not head-to-head trials)

Tandem Program[1-3]	DEPICT Program[4,5,6]	EASE Program[7]
Adjudicated DKA was characterised as:	Adjudicated DKA was characterised as:	Adjudicated DKA was characterised as:
Yes, with certainty	Definite	Certain
Yes, probably	Possible	Potential
No, unlikely	Unlikely	Ketosis (not DKA)
No, with certainty	Only "definite" was adjudicated positively as a DKA even.	Unlikely
Unclassifiable		Unclassifiable
Insufficient data		
"yes, with certainty" and "yes, probably" were both adjudicated positively as a DKA event		

DKA=diabetic ketoacidosis

References: 1. Buse B, et al. Diabetes Care 2018;41:1970−80 & Supplementary Appendix; 2. Danne T, et al. Diabetes Care 2018;41:1981−90 & Supplementary Appendix. 3. Garg SK et al. *N Engl J Med*. 2017;377:2337–2348
4. Dandona P, et al. Lancet Diabetes Endocrinol 2017;5:864−76. 5. Mathieu C, et al. Diabetes Care 2018;41:1938−46.6. Dandona et al. Diabetes Care. 2018 Oct 23. pii: dc181087. doi: 10.2337/dc18-1087 7. Rosenstock J, et al. Diabetes Care 2018; doi.org/10.2337/dc18-1749.

SUPPLEMENTARY DATA

Supplementary Table 2. Incidence of reported DKA from Tandem1 and Tandem2

A. Diabetic ketoacidosis at 24 weeks inTandem1 and inTandem2

	inTandem1[1]			inTandem2[2]		
Dose	**PBO**	**SOTA 200 mg**	**SOTA 400 mg**	**PBO**	**SOTA 200 mg**	**SOTA 400 mg**
N	268	263	262	258	261	263
Patients with ≥1 Certain DKA event	0	3	8	0	2	3
Patients with ≥1 Probable DKA event	0	0	0	0	0	1
Certain + Probable DKA	0	3	8	0	2	4
% Patients with ≥1 Certain+ Probable DKA	0	1.1	3.1	0	0.8	1.5
% difference versus placebo in patients with Certain+ Probable DKA*	N/A	1.1	3.1	N/A	0.8	1.5

DKA=diabetic ketoacidosis; PBO=placebo; SOTA= sotagliflozin

SUPPLEMENTARY DATA

B. Diabetic ketoacidosis at 52 weeks inTandem1 and inTandem2

	inTandem1[1]			inTandem2[2]			Total inTandem1 & 2[3]		
Dose	**PBO**	**SOTA 200 mg**	**SOTA 400 mg**	**PBO**	**SOTA 200 mg**	**SOTA 400 mg**	**PBO**	**SOTA 200 mg**	**SOTA 400 mg**
N	268	263	262	258	261	263	526	524	525
Patients with ≥1 Certain DKA event	0	9	11	0	5	8	0	14	19
Patients with ≥1 Probable DKA event	1	0	0	0	1	1	1	1	1
Certain + Probable DKA	1	9	11	0	6	9	1	15	20
% Patients with ≥1 Certain+ Probable DKA	0.4	3.4	4.2	0	2.3	3.4	0.2	2.9	3.8
% difference versus placebo of patients with Certain+ Probable DKA*	N/A	3.0	3.8	N/A	2.3	3.4	N/A	2.7	3.6

DKA=diabetic ketoacidosis; PBO=placebo; SOTA= sotagliflozin

References: 1. Buse B, et al. Diabetes Care 2018;41:1970−80 & Supplementary Appendix; 2. Danne T, et al. Diabetes Care 2018;41:1981−90 & Supplementary Appendix. 3. Garg SK et al. *N Engl J Med*. 2017;377:2337–2348.

SUPPLEMENTARY DATA

Supplementary Table 3. Diabetic ketoacidosis in DEPICT-1 and DEPICT-2

A. Diabetic ketoacidosis at 24 weeks in DEPICT-1 und DEPICT-2

	DEPICT-1[1]			DEPICT-2[2]		
Dose	**PBO**	**DAPA 5 mg**	**DAPA 10 mg**	**PBO**	**DAPA 5 mg**	**DAPA 10 mg**
N	260	277	296	272	271	270
Patients with ≥1 Definite DKA	3	4	5	0	7	6
Patients with ≥1 Possible DKA	1	5	7	2	6	4
Patients with ≥1 Unlikely DKA	3	8	8	7	8	4
% Patients with DKA as defined in the protocol (definite DKA)*	**1.2**	**1.4**	**1.7**	**0**	**2.6**	**2.2**
% difference versus placebo of patients with DKA as defined in the protocol (definite DKA)*	**N/A**	**0.2**	**0.5**	**N/A**	**2.6**	**2.2**

DKA=diabetic ketoacidosis; PBO=placebo; DAPA= dapagliflozin

SUPPLEMENTARY DATA

B. Diabetic ketoacidosis at 52 weeks in DEPICT-1

	DEPICT-1[1]		
Dose	**PBO**	**DAPA 5 mg**	**DAPA 10 mg**
N	260	277	296
Patients with ≥1 Definite DKA	5	11	10
Patients with ≥1 Possible DKA	2	8	9
Patients with ≥1 Unlikely DKA	3	9	11
% Patients with DKA as defined in the protocol (definite DKA)*	**1.9**	**4.0**	**3.4**
% difference versus placebo of patients with DKA as defined in the protocol (definite DKA)	**N/A**	**2.1**	**1.5**

DKA=diabetic ketoacidosis; PBO=placebo; DAPA= dapagliflozin

References: Dandona et al. Lancet Diabetes Endocrinol. 2017 Nov;5(11):864-876; Mathieu C et al. DEPICT-2 Investigators. Diabetes Care. 2018 Sep;41(9):1938-1946. Dandona et al. Diabetes Care. 2018 Oct 23. pii: dc181087. doi: 10.2337/dc18-1087.

SUPPLEMENTARY DATA

Supplementary Table 4. Diabetic ketoacidosis at 26 and 52 weeks: EASE-2 and EASE-3

	EASE-2 & -3 pooled* (EASE-2 up to 52 Weeks; EASE-3 up to 26 Weeks)			EASE-3 26 Weeks	
Dose	**PBO**	**EMPA 10 mg**	**EMPA 25 mg**	**PBO**	**EMPA 2.5 mg**
N	484	491	489	241	241
Patients with ≥1 Certain** DKA (n/%)	6 (1.2)	16 (3.3)	21 (4.3)	3 (1.2)	2 (0.8)
Patients with ≥1 Potential*** DKA (n/%)	6 (1.2)	13 (2.7)	15 (3.1)	1 (0.4)	3 (1.2)

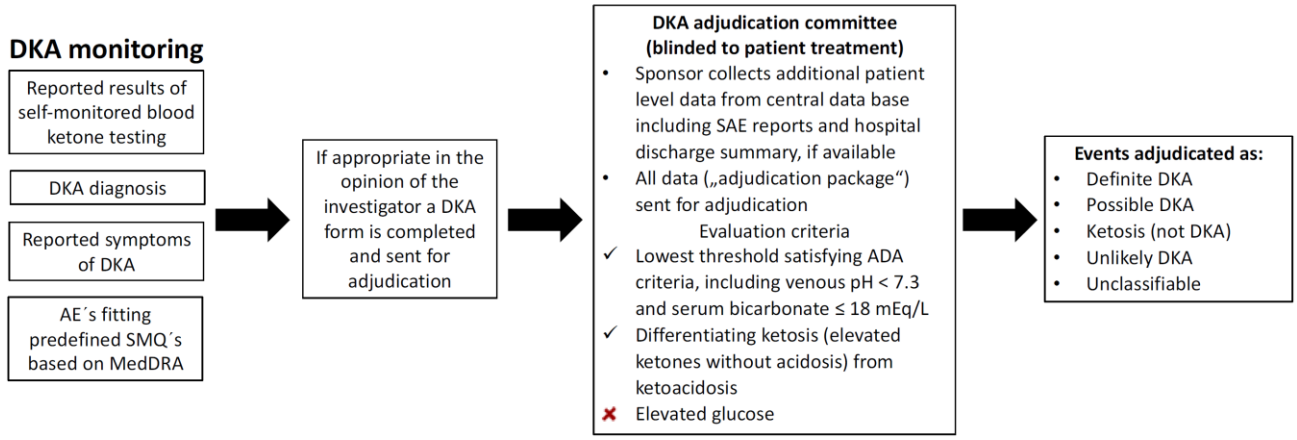
DKA=diabetic ketoacidosis; PBO=placebo; DAPA= empagliflozin

Results from adjudication based on broad trigger search criteria (1. Investigator reported terms indicative of DKA; 2. All BHB readings >1.5 and < 3.8 mmol/l and clinical manifestations suggestive of ketoacidosis; 3. Any BHB reading ≥3.8 mmol/l). *Definition certain ketoacidosis: Acidosis and ketosis present; ** Definition potential ketoacidosis: Acidosis or ketosis with clinical manifestations suggestive of ketoacidosis

Reference: Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: The EASE Trials. Diabetes Care. 2018;41(12):2560-2569.

SUPPLEMENTARY DATA

Supplementary Figure 1. Process for DKA monitoring and adjudication in studies.

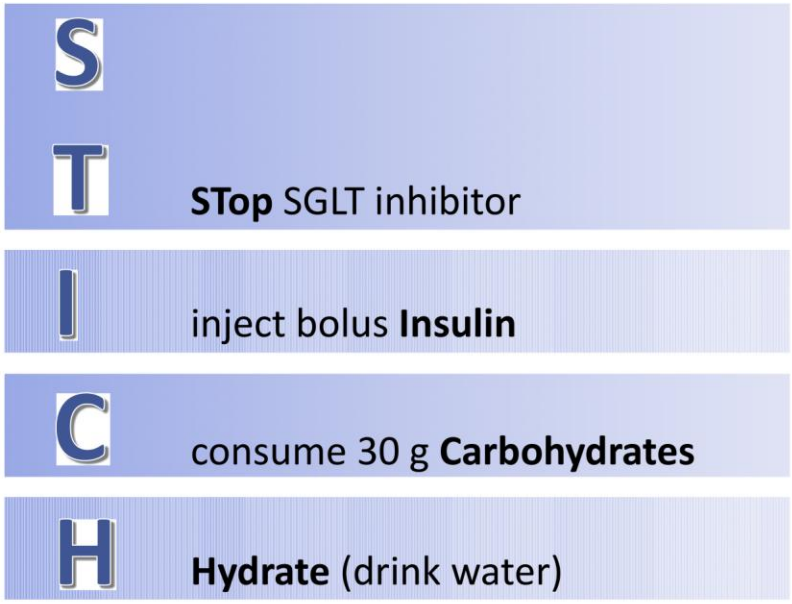


medDRA = medical Dictionary for Regulatory Activities; SMQ= standardized MedDRA query)

SUPPLEMENTARY DATA

Supplementary Figure 2. Sample wallet card. (A) front of card, (B) back of card.

A



Please carry this card if you are using a SGLT inhibitor with insulin to treat diabetes

B

Diabetic ketoacidosis (DKA) is always preceded by ketosis. It is possible that in patients taking SGLT inhibitors, ketosis or DKA may present with nonspecific or vague symptoms, and normal blood glucose levels, rather than high blood glucose, which is traditionally associated with DKA. Symptoms may include abdominal pain, nausea, vomiting, fatigue, and/or dyspnea. When DKA is suspected, β-hydroxybutyrate measurements (preferred) or urine ketones should be performed.

To correct ketosis or acidosis, it is vital to ensure that rapid acting insulin is administered frequently regardless of blood sugar levels (even if blood sugar is not elevated). Glucose-containing foods or liquids should be given when this extra insulin is administered.

Patient name: _____

If any problems occur, please contact:

Emergency contact: _____ Phone: _____

Physician name: _____ Phone: _____

(Reference: Garg et al.Diabetes Technol Ther. 2018 Sep;20(9):571-575.)