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Supplementary Table 1. Complete list of inclusion and exclusion criteria

Inclusion criteria
1. Provision of written informed consent
2. Men and women of age 18–75 years
3. Diagnosis of type 1 diabetes and central laboratory test of C-peptide <0.7 ng/mL (or <0.23 nmol/L)
4. Insulin usage for ≥12 months, and 1. No change in method of insulin administration method (MDI or CSII) for ≥3 months prior to the screening visit 2. Patients must be on a total insulin dose of ≥0.3 U/kg/day for ≥3 months prior to the screening visit 3. If on MDI insulin administration, patients must be receiving ≥3 injections/day
5. HbA1c between 7.7% and 11·0% at screening visit, and 7.5% and 10.5% at the Week-1 visit*
6. BMI ≥18.5 kg/m^2
7. Women of childbearing potential must have a negative serum or urine pregnancy test† in 24 hours prior to the start of the study treatment
8. Men and non-postmenopausal women must have agreed to the use of highly effective contraception
Exclusion criteria
Medical history
1. Type 2 diabetes
2. History of a) Maturity onset diabetes of young, pancreatic surgery or chronic pancreatitis or other pancreatic disorders that could result in decreased β-cell capacity (i.e., pancreatogenous diabetes) b) DKA requiring medical intervention (i.e., emergency room visit and/or hospitalization) within 1 month prior to the screening visit c) Hospital admission for glycemic control (hyperglycemia or hypoglycemia) within 1 month prior to the screening visit d) Addison's disease or chronic adrenal insufficiency

   e) Diabetes insipidus
   f) Bariatric surgery or lap-band procedure within 12 months prior to screening
3. Frequent episodes of severe hypoglycemia‡
4. Symptoms of poorly controlled diabetes including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during 3 months prior to the screening visit, or other signs and symptoms of poor glycemic control
5. Patients currently abusing alcohol or other drugs or who had done so in the 6 months prior to the Day-1 visit

Prohibited medications

1. Previous use of dapagliflozin and/or any other SGLT2 inhibitors
2. Use of any daily GLP-1 receptor agonist for ≥1 month or weekly GLP-1 receptor agonist for ≥2 months prior to the screening visit
3. Use of insulin-sensitizing agents, such as metformin and/or thiazolidinediones, within 2 months prior to the screening visit
4. Replacement or chronic systemic corticosteroid therapy§
5. Administration of any other investigational drug within 30 days of the screening visit

Concurrent diseases

1. Any of the following cardiovascular diseases within 6 months of the screening visit:
   a) Myocardial infarction
   b) Cardiac surgery or revascularization (coronary artery bypass surgery/percutaneous transluminal coronary angioplasty)
   c) Unstable angina
   d) Unstable CHF
   e) NYHA CHF Class III or IV
   f) Transient ischemic attack or significant cerebrovascular disease
   g) Unstable or previously undiagnosed arrhythmia
2. History of
   a) Unstable or rapidly progressing renal disease, conditions of congenital renal glucosuria, or renal allograft
   b) Hemoglobinopathy with the exception of sickle cell trait, thalassemia minor, chronic, or recurrent hemolysis

c) Bladder cancer
d) Radiation therapy to the lower abdomen or pelvis at any time

3. Significant hepatic disease, including but not limited to chronic active hepatitis and/or severe hepatic insufficiency
4. Malignancy within 5 years of the screening visit, with the exception of treated basal cell carcinoma or treated squamous cell carcinoma
5. Known immunocompromised status, including but not limited to individuals who have undergone organ transplantation or are HIV positive
6. Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring the withdrawal of >400 mL of blood during the 8 weeks prior to the screening visit

Laboratory findings

1. The following laboratory findings:
    a) Aspartate aminotransferase >3× ULN normal
    b) Alanine aminotransferase >3× ULN
    c) Serum total bilirubin >2× ULN, unless exclusively caused by Gilbert's Syndrome
    d) Calculated creatinine clearance <60 mL/min
    e) Hemoglobin ≤11.0 g/dL (110 g/L) for men and ≤10.0 g/dL (100 g/L) for women
    f) Positive for hepatitis B surface antigen or anti-hepatitis C virus antibody
    g) Abnormal Free T4

Other

1. Allergies or contraindication to the contents of dapagliflozin tablets or insulin
2. Women who are pregnant or breastfeeding
3. Prisoners or patients involuntarily incarcerated or detained, including for treatment of psychiatric or physical illness
4. Patients undergoing a commercial weight loss program with ongoing weight loss, or on an intensive exercise programme
5. Any unstable endocrine, psychiatric, or rheumatic disorders as judged by the Investigator

6. Patients at risk of volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, who could not carefully monitor their volume status

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*as measured by the central laboratory; one-time repeat HbA1c test for patients in screening was allowed if their initial test result was ±0.2% of the cut-off values).

†Minimum sensitivity 25 IU/L or equivalent HCG units.

‡Defined as more than one episode requiring medical assistance, emergency care (paramedics or emergency room care), and/or glucagon therapy administered by a third-party individual within 1 month prior to the screening visit.

§Defined as any dose of systemic corticosteroid (including local injections such as intramuscular or intra-articular etc.) taken for >4 weeks within 3 months prior to the Day-1 visit; topical or inhaled corticosteroids were allowed.

BMI, body mass index; CHF, congestive heart failure; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; MDI, multiple daily injections; NYHA, New York Heart Association; SD, standard deviation; SGLT2, sodium-glucose cotransporter type 2; ULN, upper limit of normal.

SUPPLEMENTARY DATA

Supplementary Table 2. Additional details about study methodology

Diabetes management

4. Diabetes management included glycemic control and monitoring glycemic variability and frequency of hypoglycemic events.
5. Patients were provided counselling for diet and exercise throughout the lead-in and treatment periods

Randomization stratification

Randomization was stratified on the following basis:

6. Current use of continuous glucose monitoring
7. Method of insulin administration: MDI versus CSII
8. Baseline (Week –1) HbA1c (7.5–<9.0% versus 9.0–10.5% [58–<75 mmol/mol versus 75–91 mmol/mol])

Visit schedule

g) During the lead-in period, visits were scheduled at Weeks –8, –4, –2, and –1 (Week –4 could be an optional phone visit)

h) During the study period, visits occurred on Day 1 and at Weeks 1, 2, 4, 8, 10, 12, 18, 22, and 24 (Weeks 2, 10 and 22 could be optional phone visits)

i) Telephone visits occurred on Days 2, 4, and 10

j) HbA1c was recorded at Weeks 4, 8, 12, 18, and 24; total daily insulin dose at Weeks 2, 12, and 24; and body weight on Day 1 and at Weeks 1, 2, 4, 8, 12, 18, and 24

Insulin dose adjustment

h) Insulin doses were adjusted as deemed appropriate by the investigator, based on CGM or SMBG readings (recommended 4 times/day at a minimum and 6 times/day during protocol specified periods of intense glucose monitoring), local guidance, and individual circumstances

i) In patients on CGM, sensor data were used for to make insulin dose adjustments

Change in Insulin administration method

h) Patients were not allowed to change their insulin administration method (MDI or CSII) during the study unless a patient needed to replace an insulin pump

i) In such cases, a temporary switch (<2 weeks) to MDI was allowed, with CSII administration restarting as soon as possible

Brief instructions for use of blood ketone meters

e) Patients were trained in the procedure of conducting blood ketone testing according to the manufacturer's specifications

f) Patients were advised to measure their blood ketones on experiencing potential symptoms/signs of DKA, including but not limited to: excessive thirst, nausea and vomiting, frequent urination, weakness or fatigue, fever, fruity-scented breath, confusion, and/or consistently elevated blood glucose, and/or during acute illness

g) Ketone measurement should be done if symptoms occur, regardless of plasma glucose values

h) Blood ketone test results, symptoms potentially associated with DKA, and relevant risk factors (eg, missed insulin injection, insulin pump malfunction, infection, heart attack, etc) should be recorded

CGM assessments

- Sample collection was done for BL (Weeks −2 to −1), Weeks 10 to 12, and Weeks 22 to 24
- The electronic CGM sensor measured the patient's interstitial glucose level using electrodes to measure an electric signal produced by glucose oxidase reaction, recoding data approximately every 5 minutes
- The CGM sensor was inserted subcutaneously at Weeks −2 and −1 visits and removed prior to the first dose on the Day 1 visit, and at Weeks 10 and 22 visits to allow for monitoring of a 2 week time period
- During these periods, patients were required to document their three main meal times in the diary every day

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; MDI, multiple daily injections;

SUPPLEMENTARY DATA

Supplementary Table 3. Sensitivity analysis using multiple imputation for patients discontinuing treatment early

	Dapagliflozin 5 mg + Insulin (n=273)	Dapagliflozin 10 mg + Insulin (n=270)	Placebo + Insulin (n=272)
Adjusted mean change from baseline (SE)	–0.28 (0.06)	–0.34 (0.05)	0.04 (0.06)
Difference from placebo (95% CI)	–0.32 (–0.45, –0.19)	–0.39 (–0.52, –0.25)	
p-value*	<0.0001	<0.0001	

All data before the start of long-term dose are included. Analysis is based on an ANCOVA model with treatment group as an effect, and stratum and baseline values as covariates. Analysis is repeated on 1000 imputed datasets, and results combined using Rubin's formula. For patients who discontinued treatment early and did not have HbA1c measurements at Week 24, their Week 24 HbA1c values are imputed based on the data from those retrieved patients in the same treatment group, i.e. those who discontinued treatment early but had HbA1c measurements at Week 24, using a multiple imputation approach. *Nominal p-value.

SUPPLEMENTARY DATA

Supplementary Table 4. Change in HbA1c (%) from baseline to Week 24 (evaluation in subgroups by use of personal CGM)

Subgroup statistics	**Dapagliflozin 5 mg + Insulin (n=271)**	**Dapagliflozin 10 mg + Insulin (n=270)**	**Placebo + Insulin (n=272)**
For patients using personal CGM			
n*	87	85	83
n†	82	80	74
Baseline mean (SD)	8.41 (0.66)	8.30 (0.66)	8.32 (0.62)
Week 24 mean (SD)	8.07 (0.81)	7.95 (0.76)	8.25 (0.85)
Adjusted mean change from baseline (SE)	−0.34 (0.07)	−0.34 (0.07)	−0.11 (0.08)
Difference from placebo (95% CI)	− 0.23 (−0.43, −0.03)	−0.23 (−0.44, −0.03)	
For patients not using personal CGM			
n*	179	182	184
n†	163	165	165
Baseline mean (SD)	8.46 (0.71)	8.47 (0.69)	8.46 (0.64)
Week 24 mean (SD)	8.10 (0.86)	8.01 (0.76)	8.52 (0.85)
Adjusted mean change from baseline (SE)	−0.34 (0.05)	−0.40 (0.05)	−0.10 (0.05)
Difference from placebo (95% CI)	− 0.44 (−0.58, −0.30)	−0.50 (−0.64, −0.36)	
Use of CGM interaction test p-value‡ = 0.0269			

*Number of patients in full analysis dataset with non-missing baseline and at least one post-baseline value. †Number of patients in full analysis dataset with non-missing baseline and Week 24 values. P-value for the treatment-by-subgroup interaction based on average treatment effect vs. control across subgroups at Week 24.
CGM, continuous glucose monitoring, CI, confidence intervals; SD, standard deviation; SE, standard error

SUPPLEMENTARY DATA

Supplementary Table 5. Change in HbA1c (%) from baseline to Week 24 (evaluation in subgroups by method of insulin administration)

Subgroup statistics	**Dapagliflozin 5 mg + Insulin (n=271)**	**Dapagliflozin 10 mg + Insulin (n=270)**	**Placebo + Insulin (n=272)**
CSII			
n*	90	92	91
n†	82	86	76
Baseline mean (SD)	8.38 (0.66)	8.40 (0.61)	8.38 (0.65)
Week 24 mean (SD)	8.00 (0.71)	8.04 (0.82)	8.29 (0.87)
Adjusted mean change from baseline (SE)	−0.35 (0.07)	−0.35 (0.07)	−0.06 (0.07)
Difference from placebo (95% CI)	− 0.28 (−0.48, −0.09)	−0.29 (−0.48, −0.09)	
MDI			
n*	176	175	176
n†	163	159	163
Baseline mean (SD)	8.48 (0.71)	8.43 (0.73)	8.43 (0.63)
Week 24 mean (SD)	8.14 (0.90)	7.96 (0.73)	8.50 (0.85)
Adjusted mean change from baseline (SE)	−0.31 (0.05)	−0.39(0.05)	0.10 (0.05)
Difference from placebo (95% CI)	− 0.41 (−0.55, −0.28)	−0.49 (−0.63, −0.35)	
Use of CGM interaction test p-value‡ = 0.1209			

*Number of patients in full analysis dataset with non-missing baseline and at least one post-baseline value. †Number of patients in full analysis dataset with non-missing baseline and Week 24 values. P-value for the treatment-by-subgroup interaction based on average treatment effect vs. control across subgroups at Week 24.
CGM, continuous glucose monitoring, CI, confidence intervals; SD, standard deviation; SE, standard error

Supplementary Table 6. Change in CGM mean glucose values and MAGE

	Dapagliflozin 5 mg + Insulin (n=271)	Dapagliflozin 10 mg + Insulin (n=270)	Placebo + Insulin (n=272)
24-h CGM mean value (mg/dL)			
N*	252	255	257
Baseline mean (SD)	192.67 (28.68)	191.53 (28.09)	190.89 (28.95)
Week 24 mean (SD)	181.49 (32.93)	176.01 (26.52)	195.73 (31.04)
Adjusted mean change from baseline (SE)	–6.46 (1.83)	–10.54 (1.83)	9.20 (1.85)
Difference from placebo (95% CI)	–15.66 (–20.26, –11.05)	–19.74 (–24.34, –15.14)	
p-value†	<0.0001	<0.0001	
24-h CGM MAGE (mg/dL)			
N*	252	255	257
Baseline mean (SD)	169.35 (29.60)	171.02 (29.85)	168.38 (29.29)
Week 24 mean (SD)	156.98 (33.89)	158.17 (35.69)	165.82 (28.22)
Adjusted mean change from baseline (SE)	–10.17 (1.90)	–9.68 (1.91)	–0.33 (1.93)
Difference from placebo (95% CI)	–9.85 (–14.66, –5.03)	–9.36 (–14.16, –4.55)	
p-value†	<0.0001	0.0001	
24-h CGM values within >70 mg/dL to ≤180 mg/dL (%)			
N*	252	255	257
Baseline mean (SD)	43.50 (12.43)	43.68 (11.83)	43.52 (12.55)
Week 24 mean (SD)	51.12 (14.15)	53.22 (13.39)	42.40 (13.23)

Adjusted mean change from baseline (SE)	5.92 (0.82)	7.60 (0.82)	–3.10 (0.83)
Difference from placebo (95% CI)	9.02 (6.97, 11.06)	10.70 (8.66, 12.74)	
p-value†	<0.0001	<0.0001	
24-H CGM values within ≤70 mg/dL (%)			
N*	252	255	257
Baseline mean (SD)	4.76 (4.31)	5.12 (4.78)	5.24 (6.17)
Week 24 mean (SD)	4.77 (4.52)	5.19 (4.22)	4.47 (4.15)
Adjusted mean change from baseline (SE)	−0.37 (0.28)	−0.14 (0.28)	−0.84 (0.28)
Difference from placebo (95% CI)	0.46 (−0.23, 1.16)	0.70 (0.00, 1.39)	
p-value‡	NA	NA	

*N is the number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value. †Nominal p-value. ‡p-values were not calculated for exploratory endpoints such as this.

CI, confidence interval; CGM, continuous glucose monitoring; MAGE, mean amplitude of glucose excursion, NA, not available; SD, standard deviation; SE, standard error

Supplementary Table 7. Summary of recurrent hypoglycemic events

	Dapagliflozin 5 mg + Insulin (n=271) (120.0 patient-years)	Dapagliflozin 10 mg + Insulin (n=270) (120.1 patient-years)	Placebo + Insulin (n=272) (119.2 patient-years)
Total number of hypoglycemic events	4725	4891	4579
Total number of patients experiencing ≥1 hypoglycemic event,[a] n (%)	223 (82.3%)	231 (85.6%)	234 (86.0%)
Exposure adjusted incidence rate[b]	3935.97	4070.91	3842.40
ADA categorization			
Severe hypoglycemia			
Total number of event,[c] n (%)	58 (1.2%)	55 (1.1%)	51 (1.1%)
Total number of patients experiencing ≥1 hypoglycemic event,[a] n (%)	17 (6.3%)	23 (8.5%)	21 (7.7%)
Exposure adjusted incidence rate[b]	48.31	45.78	42.80
Documented symptomatic hypoglycemia			
Total number of event,[c] n (%)	3550 (75.1%)	3769 (77.1%)	3526 (77.0%)
Total number of patients experiencing ≥1 hypoglycemic event,[a] n (%)	216 (79.7%)	214 (79.3%)	222 (81.6%)
Exposure adjusted incidence rate[b]	2957.19	3137.04	2958.79
Asymptomatic hypoglycemia			
Total number of event,[c] n (%)	920 (19.5%)	959 (19.6%)	858 (18.7%)

Total number of patients experiencing ≥1 hypoglycemic event,[a] n (%)	100 (36.9%)	127 (47.0%)	98 (36.0%)
Exposure adjusted incidence rate[b]	766.37	798.20	719.98
Probable symptomatic hypoglycemia			
Total number of event,[c] n (%)	65 (1.4%)	57 (1.2%)	82 (1.8%)
Total number of patients experiencing ≥1 hypoglycemic event,[a] n (%)	20 (7.4%)	29 (10.7%)	27 (9.9%)
Exposure adjusted incidence rate[b]	54.15	47.44	68.81
Relative hypoglycemia			
Total number of event,[c] n (%)	82 (1.7%)	41 (0.8%)	56 (1.2%)
Total number of patients experiencing ≥1 hypoglycemic event,[a] n (%)	19 (7.0%)	17 (6.3%)	20 (7.4%)
Exposure adjusted incidence rate[b]	68.31	34.13	46.99
Other hypoglycemia			
Total number of event,[c] n (%)	50 (1.1%)	10 (0.2%)	6 (0.1%)
Total number of patients experiencing ≥1 hypoglycemic event,[a] n	6 (2.2%)	7 (2.6%)	5 (1.8%)

(%)			
Exposure adjusted incidence rate[b]	41.65	8.32	5.03

Includes hypoglycemia events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days or up to the start of the long-term if earlier. [a]Percentages are based on the total number of subjects in safety analysis set; [b]Exposure adjusted incidence rate per 100 person-years including recurrences; [c]Percentages are based on the total number of events.

ADA, American Diabetes Association

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Supplementary Table 8. Number of self-monitored blood ketone measurements

	Dapagliflozin 5 mg + Insulin (n=271)	Dapagliflozin 10 mg + Insulin (n=270)	Placebo + Insulin (n=272)
n*	197	186	193
Number of self-monitored blood ketone measurements	2993	3529	4373
Number of self-monitored blood ketone measurements >3.0 mmol/L	18	21	7
Mean number of self-monitored blood ketone measurements per day per patient (SD)	1.21 (0.70)	1.17 (0.53)	1.23 (0.63)

n* is the number of subjects in safety analysis set with at least one ketones assessment during short-term double-blind treatment period.

SD, standard deviation

Supplementary Table 9. Listing of maximum ketone values for patients with definite DKA events

Patient No	Treatment	Maximum BOHB value (mmol/L)	Number of ketone measurements prior to or on the same day as the event
1	DAPA 5 mg + INS	5.8	4
2	DAPA 5 mg + INS	4.3	1
3	DAPA 5 mg + INS	6.3	5
4	DAPA 5 mg + INS	4.6	9
5	DAPA 5 mg + INS	2.9	5
6	DAPA 5 mg + INS	NA	13
7	DAPA 5 mg + INS	NA	0
8	DAPA 10 mg + INS	5.0	1
9	DAPA 10 mg + INS	2.2	3
10	DAPA 10 mg + INS	7.2	2
11	DAPA 10 mg + INS	NA	0
12	DAPA 10 mg + INS	NA	0
13	DAPA 10 mg + INS	NA	0

BOHB, beta-hydroxybutyrate, DKA, diabetic ketoacidosis; DAPA, dapagliflozin; INS, insulin; NA, not available

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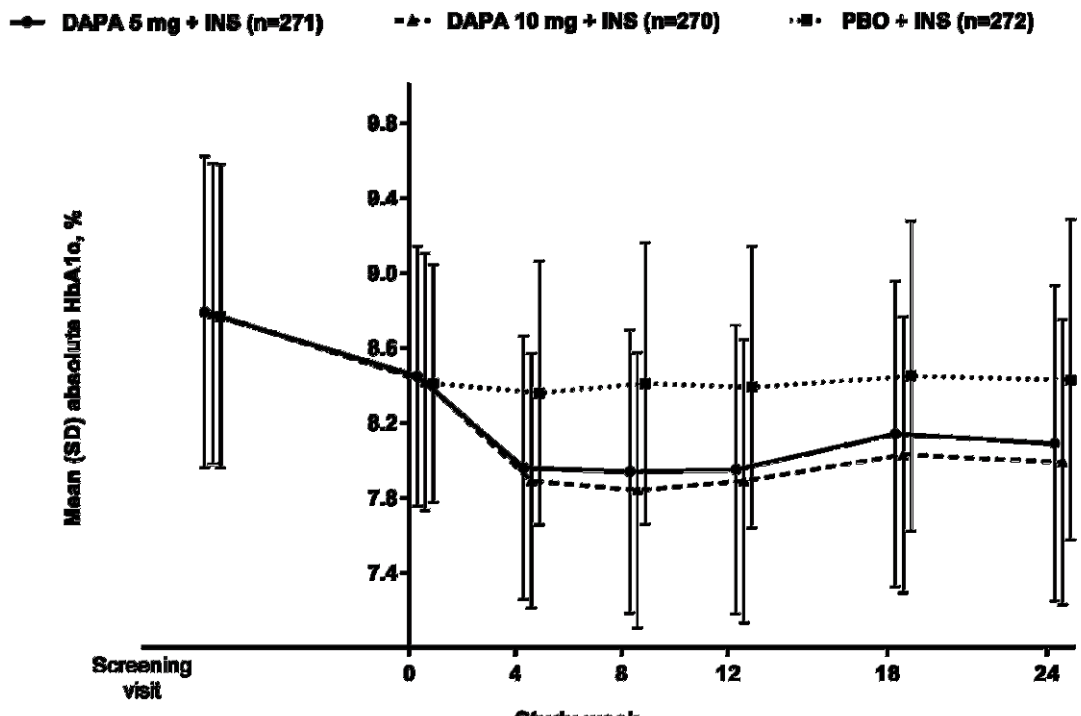
Supplementary Figure 1. Absolute mean (SD) HbA1c (%) over 24 weeks



Patients per timepoint							
DAPA 5 mg + INS	271	266	265	258	253	250	245
DAPA 10 mg + INS	269	267	264	261	257	246	245
PBO + INS	270	267	265	260	258	246	239

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Supplementary Appendix. List of DEPICT-2 Principal Investigators

Argentina:

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