SUPPLEMENTARY DATA

Detailed inclusion and exclusion criteria

Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects must be willing and able to give signed and dated written informed consent.

2) Target Population

a) Subject must have type 1 diabetes with inadequate glycemic control, defined as central laboratory A1C ≥ 7.0% and ≤ 10.0%, obtained at the screening visit (Note: A one-time central laboratory re-test of the A1C is allowed in subjects with an initial central laboratory A1C of 6.8% or 10.2% who are otherwise eligible, as determined by the Investigator.)
b) Insulin use, either multiple doses (at least 2x/day) of insulin consisting of long-acting (glargine or detemir) plus short-acting prandial insulin or on insulin pump (continuous subcutaneous insulin infusion, CSII), for at least 12 months and initiation of insulin immediately after diagnosis of diabetes. [Method of insulin administration (multiple daily injections or CSII) must have been stable for at least 3 months prior to Day −3. In addition, the dose of basal insulin must have remained stable (within 20% variance of the total daily dose) for the 2 weeks preceding Day −3 (per subject report)].
c) Central laboratory C-peptide value of < 0.7 ng/mL at screening.
d) BMI 18.5 to 35.0 kg/m^2, inclusive at screening.

2) Age and Reproductive Status

a) Men and women, ages 18 to 65 years old.
b) Women of childbearing potential (WOCBP) and men must be using an acceptable method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized.
c) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.
d) Women must not be breastfeeding

Exclusion Criteria

1) Target Disease Exclusions

a) History of T2DM, maturity onset diabetes of young (MODY), pancreatic surgery or chronic pancreatitis.
b) Any use of oral hypoglycemic agents within 12 months prior to the Day −3 visit.
c) History of diabetes ketoacidosis (DKA) within 24 weeks prior to the Day −3 visit.
d) History of diabetes insipidus.
e) History of hospital admission for glycemic control (either hyperglycemia or hypoglycemia) within 6 months prior to the Day −3 visit
f) Frequent episodes of hypoglycemia as defined by more than one episode requiring assistance, emergency care (paramedics or emergency room care) or glucagon therapy, or more than 2 unexplained episodes of symptomatic hypoglycemia within 3 months prior to Day −3. An

unexplained event is defined as an event that cannot be explained by circumstances such as dietary (e.g. missed meal), strenuous exercise, error in insulin dosing, etc.

g) Hypoglycemic unawareness.
h) History of Addison's disease or chronic adrenal insufficiency.

2) Medical History and Concurrent Diseases

Any of the following CV/Vascular Diseases within 6 months of the screening visit:

a) Myocardial infarction
b) Cardiac surgery or revascularization (coronary artery bypass surgery [CABG]/percutaneous transluminal coronary angioplasty [PTCA])
c) Unstable angina
d) Unstable congestive heart failure (CHF)
e) CHF New York Heart Association (NYHA) Class III or IV
f) Transient ischemic attack (TIA) or significant cerebrovascular disease
g) Unstable or previously undiagnosed arrhythmia

3) Physical and Laboratory Test Findings

a) Aspartate aminotransferase (AST) > 2X Upper limit of normal (ULN)
b) Alanine aminotransferase (ALT) > 2X ULN
c) Serum total bilirubin > 2X ULN
d) Estimated GFR (eGFR) by the Modification of Diet in Renal Disease (MDRD) formula ≤ 60 mL/min/1.73m^2. The renal function, eGFR will be estimated by the abbreviated MDRD, using laboratory measurements of serum creatinine collected at screening [eGFR (mL/min/1.73m^2) = 175 x (standardized Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black)].
e) Hemoglobin ≤ 11.0 g/dL (110 g/L) for men; hemoglobin ≤10.0 g/dL (100 g/L) for women.
f) Creatine kinase (CK) > 3X ULN
g) Positive for hepatitis B surface antigen or anti-hepatitis C virus antibody.
h) Abnormal Free T4

Note: abnormal TSH value at screening will be further evaluated for free T4.Subjects with abnormal free T4 values will be excluded. A one-time retest may be allowed, as determined by the Investigator, after a minimum of 6 weeks following the adjustment of thyroid hormone replacement therapy in subject who have had a prior diagnosis of a thyroid disorder and who are currently receiving thyroid replacement therapy. Such cases should be discussed with the Sponsor prior to re-testing. The subject must have all screening procedures and laboratory assessments performed as part of this re-test, and all of these must meet enrollment eligibility criteria. The subject's number will, however, remain the same as initially assigned.

4) Allergies and Adverse Drug Reaction

a) Allergies or contraindication to the contents of dapagliflozin tablets or insulin.

5) Renal, Hepatic, Hemotological/Oncological Diseases/Conditions

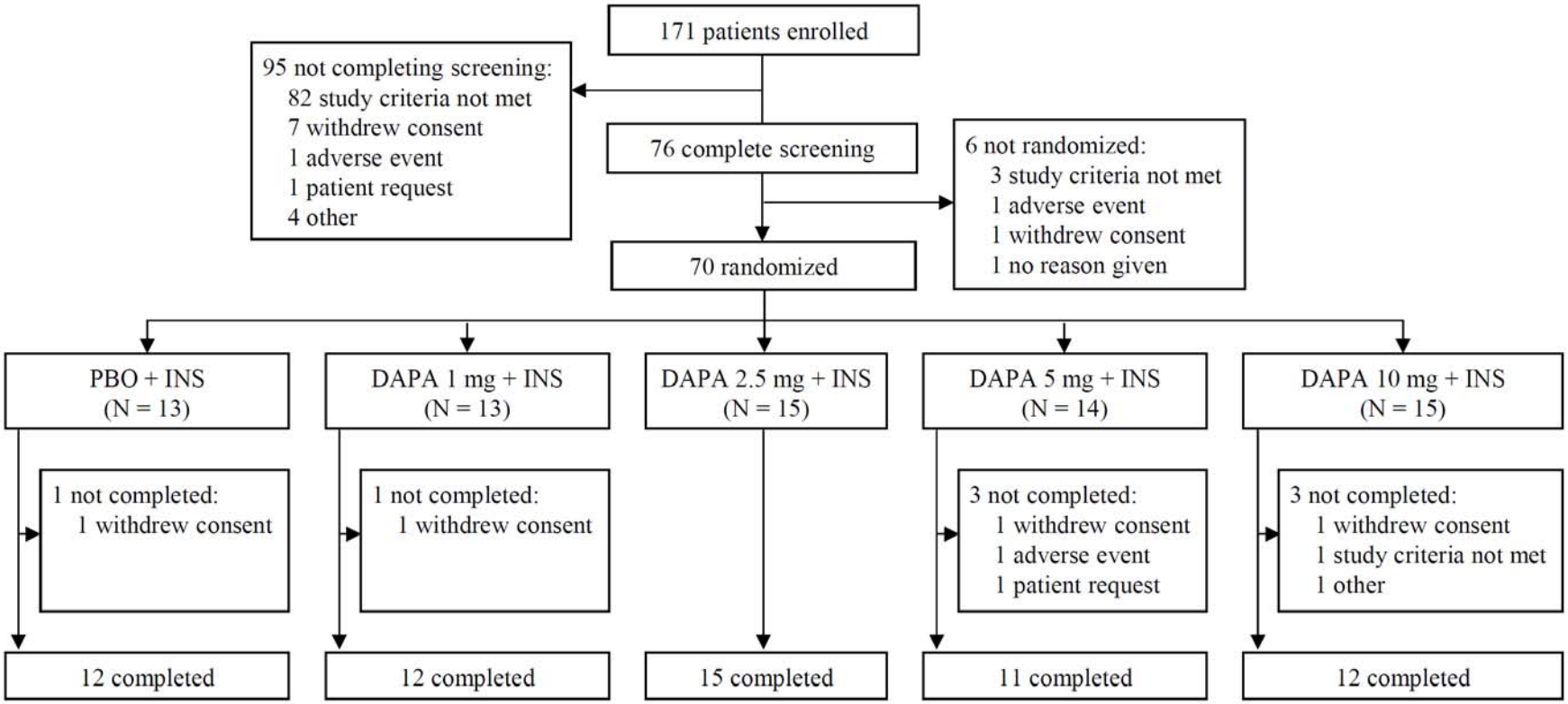
a) History of unstable or rapidly progressing renal disease.
b) Conditions of congenital renal glucosuria.
c) Renal allograft.
d) Significant hepatic disease, including but not limited to, chronic active hepatitis and/or severe hepatic insufficiency.
e) Documented history of hepatotoxicity with any medication
f) Documented history of severe hepatobiliary disease.
g) History of hemoglobinopathy, with the exception of sickle cell trait (SA) or thalassemia minor; or chronic or recurrent hemolysis.
h) Donation of blood or blood products to a blood bank, blood transfusion, or participation in a clinical study requiring withdrawal of > 400 mL of blood during the 6 weeks prior to the enrollment visit.
i) Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.
j) Malignancy within 5 years of the screening visit (with the exception of treated basal cell or treated squamous cell carcinoma of the skin)

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
c) Replacement or chronic systemic corticosteroid therapy, defined as any dose of systemic corticosteroid taken for > 4 weeks within 3 months prior to Day -3 visit.
NOTE: Topical or inhaled corticosteroids are allowed.
d) Any unstable endocrine, psychiatric, rheumatic disorders as judged by the Investigator.
e) Subject is, in the judgment of the Investigator, unlikely to comply with the protocol or has any severe concurrent medical or psychological condition that may affect the interpretation of efficacy or safety data.
f) Subject with any condition which, in the judgment of the Investigator, may render the subject unable to complete the study or which may pose a significant risk to the subject.
g) Subject is currently abusing alcohol or other drugs or has done so within the last 6 months.
h) Subject is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned.
i) Previous participation in a clinical trial with dapagliflozin (BMS-512148) and/or with any other SGLT2 inhibitors.
j) Administration of any other investigational drug within 30 days of planned enrollment to this study.
k) No clinical conditions or clinically significant abnormalities, in any laboratory value(s) collected after screening and prior to randomization which, in the Investigator's judgment, should preclude entry into the treatment period

SUPPLEMENTARY DATA

Supplementary Figure 1. Patient disposition. DAPA, dapagliflozin; INS, insulin; PBO, placebo.



SUPPLEMENTARY DATA

Supplementary Table 1. Changes in total daily fluid intake, total daily fluid output, total daily urine output, body weight and seated systolic blood pressure.

	Insulin + Placebo (N=13)	**Insulin + Dapagliflozin**			
		1 mg (N=13)	**2.5 mg (N=15)**	**5 mg (N=14)**	**10 mg (N=15)**
Total daily fluid intake, mL					
n	13	12	15	14	13
Baseline value, mean (SD)	2823 (640)	3303 (1615)	3277 (1887)	2709 (728)	2985 (1301)
Value at Day 7, mean (SD)	3966 (838)	4240 (1895)	3419 (1711)	2933 (940)	2794 (1041)
Change from baseline, mean (95% CI)	1143 (649, 1637)	926 (332, 1521)	142 (−703, 987)	224 (−228, 676)	−182 (−751, 388)
Total daily urine output, mL					
n	13	12	15	14	13
Baseline value, mean (SD)	2953 (1020)	3488 (1331)	2955 (1149)	2096 (586)	2735 (1188)
Value at Day 7, mean (SD)	3742 (1650)	3825 (1486)	3538 (1650)	2601 (862)	3081 (1007)
Change from baseline, mean (95% CI)	789 (−367, 1944)	325 (−301, 951)	584 (−369, 1536)	505 (−17, 1027)	371 (−346, 1088)
Body weight, kg					
n	13	12	15	14	13
Baseline value, mean (SD)	78.02 (11.40)	77.68 17.235	77.41 13.392	67.27 7.557	81.11 19.794
Value at Day 7, mean (SD)	78.05 (10.43)	76.63 17.050	77.11 13.159	66.38 7.501	80.45 19.704
Change from baseline, mean (95% CI)	0.02 (−0.99, 1.04)	−1.05 (−2.07, −0.03)	−0.30 (−1.24, 0.64)	−0.89 (−1.39, −0.39)	−0.66 (−1.39, 0.07)
Seated systolic BP, mm Hg					
n	13	12	15	14	13
Baseline value, mean (SD)	113.3 11.18	109.9 9.90	114.4 10.48	113.6 10.91	118.2 13.37
Value at Day 7, mean (SD)	114.7 10.06	105.8 10.28	114.6 13.84	110.8 10.04	113.2 12.90
Change from baseline, mean (95% CI)	1.4 (−2.9, 5.6)	−4.2 (−8.6, 0.3)	0.2 (−4.5, 4.9)	−2.8 (−5.6, 0.1)	−5.0 (−10.3, 0.3)

N is the number of randomized patients who took at least one dose of double-blind study medication. n is the number of randomized patients with non-missing baseline and Day 7 values. BP, blood pressure.

SUPPLEMENTARY DATA

Supplementary Table 2. Summary statistics for steady-state pharmacokinetic parameters at Day 7.

		Dapagliflozin			Dapagliflozin 3-O-glucuronide			
Treatment Group	**Statistic**	**C_{max} (ng/mL)**	**T_{max} (h)**	**AUCτ (ng*h/mL)**	**C_{max} (ng/mL)**	**T_{max} (h)**	**AUCτ (ng*h/mL)**	**Ratio of metabolite to parent AUC**
Dapagliflozin 1 mg	Mean (SD)	13.6 (6.2)	1.0 (1.0)	49.8 (11.8)	11.1 (3.5)	1.4 (0.9)	51.6 (15.4)	0.74 (0.22)
+ insulin (N=12)	GM (%CV)	12.2 (45.9)		48.4 (23.7)	10.6 (31.7)		49.6 (29.9)	0.72 (29.29)
	Median (min–max)	11.1 (3.8–24.4)	0.5 (0.4–4.0)	49.1 (31.5–67.9)	10.2 (6.5–17.6)	1.0 (0.9–4.0)	47.6 (32.4–82.8)	0.71 (0.50–1.20)
Dapagliflozin 2.5 mg	Mean (SD)	25.5 (8.3)	1.1 (0.7)	133.5 (43.1)	23.9 (10.6)	1.8 (0.9)	141.2 (50.9)	0.76 (0.25)
+ insulin (N=14)	GM (%CV)	24.2 (32.5)		127.2 (32.3)	22.0 (44.5)		132.4 (36.1)	0.73 (33.22)
	Median (min–max)	24.9 (13.9–39.1)	1.0 (0.2–3.0)	135.9 (77.0–216.0)	21.5 (12.4–47.7)	2.0 (1.0–4.0)	143.7 (64.9–237.9)	0.76 (0.40–1.30)
Dapagliflozin 5 mg	Mean (SD)	73.5 (30.2)	1.0 (0.9)	278.6 (75.9)	53.9 (23.4)	1.6 (0.9)	277.5 (92.5)	0.70 (0.18)
+ insulin (N=14)	GM (%CV)	66.1 (41.1)		269.1 (27.3)	49.2 (43.3)		262.6 (33.3)	0.68 (25.69)
	Median (min–max)	79.9 (20.6–124.0)	1.0 (0.5–4.0)	264.5 (158.7–417.7)	50.1 (17.5–112.0)	1.1 (0.8–4.0)	297.0 (148.5–436.3)	0.63 (0.50–1.10)
Dapagliflozin 10 mg	Mean (SD)	140.1 (41.1)	1.3 (1.1)	670.4 (324.0)	110.6 (29.6)	1.8 (1.6)	610.7 (241.8)	0.70 (0.23)
+ insulin (N=13)	GM(%CV)	134.3 (29.3)		600.0 (48.3)	106.7 (26.8)		567.8 (39.6)	0.66 (32.37)
	Median (min–max)	137.0 (73.4–212.0)	1.0 (0.0–4.0)	663.5 (208.5–1424.8)	110.0 (56.8–163.0)	1.0 (0.5–6.0)	546.5 (242.2–1202.2)	0.61 (0.40–1.10)

N is the number of randomized patients who took at least one dose of dapagliflozin with adequate pharmacokinetic parameter profiles. AUCτ, area under the concentration-time curve in one dosing interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GM, geometric mean; SD, standard deviation; T_{max}, time of maximum observed plasma concentration.

SUPPLEMENTARY DATA

Supplementary Table 3. Prespecified secondary objective: dapagliflozin vs placebo changes in 7-point mean glucose.

	Insulin + Placebo (N=13)	**Insulin + Dapagliflozin**			
		1 mg (N=13)	**2.5 mg (N=15)**	**5 mg (N=14)**	**10 mg (N=15)**
7-point glucose, mmol/L*					
n	13	12	12	14	12
Baseline value, mean (SD)	10.23 (2.47)	8.96 (1.71)	8.99 (2.10)	9.10 (1.57)	9.15 (2.16)
Value at Day 7, mean (SD)	9.30 (1.51)	7.91 (1.34)	8.03 (1.69)	7.81 (2.23)	8.18 (1.39)
Change from baseline, mean (95% CI)	−0.92 (−2.69, 0.85)	−1.05 (−2.39, 0.29)	−0.96 (−1.84, −0.09)	−1.30 (−2.43, −0.17)	−0.97 (−2.29, 0.35)
Difference vs placebo, mean (95% CI)		−0.13 (−2.25, 2.00)	−0.04 (−1.96, 1.88)	−0.38 (−2.33, 1.58)	−0.05 (−2.17, 2.07)

N is the number of randomized patients who took at least one dose of double-blind study medication. n is the number of randomized patients with non-missing baseline and Day 7 values. *Mean glucose based upon 7-point central laboratory glucose measurements taken before/after each meal and at bedtime.

SUPPLEMENTARY DATA

CONSORT 2010 checklist of information to include when reporting a randomized trial*

Section/Topic	Item No	Checklist item	Reported on page No (paragraph)
Title and abstract			
	1a	Identification as a randomised trial in the title	p1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p3, para1–3
	2b	Specific objectives or hypotheses	p3, para4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p4–5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	p4, para2
	4b	Settings and locations where the data were collected	p5, para1
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p4, para3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p5–6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Not applicable
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p4, para3
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p4, para3
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p4, para3
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p4, para3
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	p4, para3
	11b	If relevant, description of the similarity of interventions	p4, para3
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p6, para2
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable

SUPPLEMENTARY DATA

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p7, para1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Suppl. Fig. A1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p4, para1
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	p15 (Table 1)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1&2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	p2, p8, Fig. 1&2,
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p7, para 2, p16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p10, para1
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p10, para 2
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p9–10
Other information			
Registration	23	Registration number and name of trial registry	p1, p2, p4
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.