SUPPORTING INFORMATION

Investigation of the effect of canagliflozin on the disposition index, a marker of pancreatic beta cell function, in patients with type 2 diabetes

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Table S1 Glimepiride dose adjustment algorithm

Minimum glucose	**Maximum glucose**	
	≤179 mg/dL	**≥180 mg/dL**
≤89 mg/dL	Decrease by ≥0.25 mg	Decrease by ≥0.25 mg
90–109 mg/dL	No change	No change
110–129 mg/dL	No change	Increase by 0.25 mg
≥130 mg/dL	Increase by 0.25 mg	Increase by 0.5 mg

Table S2 Changes in disposition index and related parameters

Variable		Canagliflozin (*n* = 19)		Glimepiride (*n* = 20)		Intergroup ratio	
		Geometric mean	Ratio vs baseline	Geometric mean	Ratio vs baseline	LS mean	*P* value
DI	Baseline	0.560 (0.427, 0.734)	–	0.606 (0.461, 0.797)	–	–	–
	Post	0.600 (0.460, 0.782)	1.051 (0.824, 1.340)	0.530 (0.394, 0.712)	0.890 (0.702, 1.129)	1.180 (0.840, 1.659)	0.330
Matsuda index	Baseline	3.468 (2.536, 4.742)	–	3.747 (2.817, 4.985)	–	–	–
	Post	3.627 (2.715, 4.844)	1.042 (0.875, 1.240)	3.473 (2.458, 4.907)	0.930 (0.785, 1.102)	1.120 (0.878, 1.428)	0.352
$IAUC_{Ins0–120}$	Baseline	2328 (1799, 3012)	–	2474 (1763, 3470)	–	–	–
	Post	2288 (1664, 3147)	0.977 (0.784, 1.217)	2223 (1583, 3122)	0.904 (0.730, 1.120)	1.081 (0.795, 1.469)	0.611

$IAUC_{Glu0–120}$	Baseline	14420	–	15318	–	–	–
		(13134, 15831)		(13333, 17599)			
	Post	13833	0.94	14581	0.97	0.97	0.718
		(12261, 15608)	(0.84, 1.05)	(12901, 16478)	(0.87, 1.08)	(0.83, 1.14)	
$IAUC_{Ins0–120}$/ $IAUC_{Glu0–120}$	Baseline	0.161	–	0.161	–	–	–
		(0.123, 0.211)		(0.104, 0.251)			
	Post	0.165	1.025	0.153	0.946	1.083	0.668
		(0.117, 0.234)	(0.784, 1.340)	(0.099, 0.234)	(0.728, 1.229)	(0.745, 1.576)	

Note: Values in parentheses are the 95% confidence interval.

Abbreviations: DI, disposition index; IAUC, incremental area under the curve for glucose or insulin from 0 to 120 min.

Table S3 Vital signs and blood laboratory data

Variable	Canagliflozin		Glimepiride	
	Baseline (*n* = 20)	**Week 24 (*n* = 19)**	**Baseline (*n* = 20)**	**Week 24 (*n* = 20)**
SBP, mmHg	130.1 (14.0)	120.7 (14.4)	127.9 (15.7)	125.8 (12.7)
DBP, mmHg	79.2 (11.6)	79.1 (10.3)	79.8 (8.0)	81.5 (9.1)
Pulse rate, /min	76.3 (8.7)	75.1 (8.4)	78.9 (11.9)	76.0 (11.3)
WBC, 10^2/μL	63.8 (12.4)	65.7 (16.5)	69.9 (23.0)	61.5 (17.0)
RBC, 10^4/μL	466.9 (45.3)	496.3 (53.7)	472.2 (52.1)	472.5 (57.5)
Hemoglobin, g/dL	13.77 (1.39)	14.46 (1.64)	13.96 (1.90)	13.96 (2.09)
Hematocrit, %	41.35 (3.77)	44.01 (4.51)	41.68 (5.01)	41.71 (5.54)
BUN, mg/dL	15.7 (4.1)	17.5 (4.0)	15.0 (4.4)	15.8 (4.5)
Creatinine, mg/dL	0.650 (0.208)	0.687 (0.227)	0.657 (0.182)	0.657 (0.208)
eGFR, mL/min/1.73 m^2	90.10 (22.56)	84.75 (22.83)	90.18 (21.58)	91.25 (23.64)
AST, U/L	26.5 (10.4)	22.2 (5.9)	29.6 (14.6)	35.2 (28.0)
ALT, U/L	28.1 (17.8)	21.2 (11.8)	30.8 (24.8)	36.4 (39.1)
Acetoacetate, μmol/L	60.2 (34.2)	139.2 (90.7)	66.2 (41.2)	64.5 (24.1)
3-Hydroxylbutyric acid, μmol/L	79.2 (50.4)	274.2 (264.9)	94.7 (97.4)	90.8 (66.1)
Total ketone bodies, μmol/L	139.4 (81.7)	413.4 (352.7)	160.9 (137.6)	155.3 (87.6)

Note: Values are mean (SD).

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; RBC, red blood cell count; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

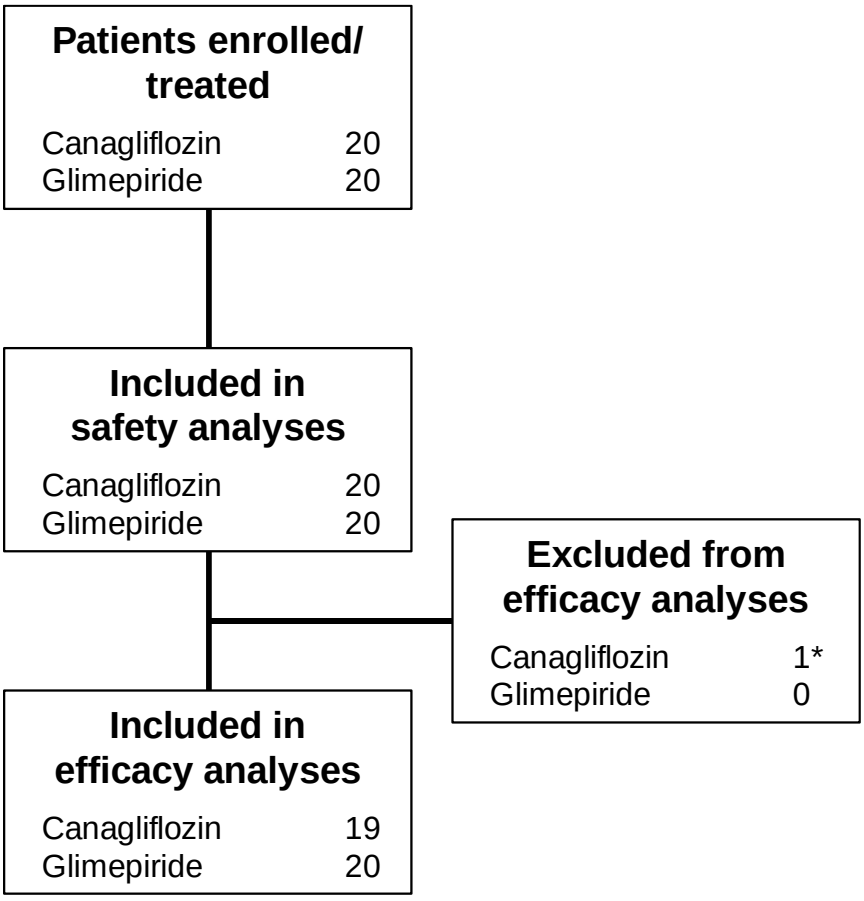
Table S4 Adverse events

	Canagliflozin (*n* = 20)	**Glimepiride (*n* = 20)**
AEs	20 (100.0%)	18 (90.0%)
SAEs	1 (5.0%)	1 (5.0%)
ADRs	15 (75.0%)	15 (75.0%)
AEs in ≥2 patients in either group		
Hypoglycemia	12 (60.0%)	14 (70.0%)
Blood ketone body increased	6 (30.0%)	0 (0.0%)
Nasopharyngitis	3 (15.0%)	5 (25.0%)
Back pain	2 (10.0%)	3 (15.0%)
Pain in extremity	2 (10.0%)	2 (10.0%)
Pruritus genital	3 (15.0%)	0 (0.0%)
Oropharyngeal pain	0 (0.0%)	3 (15.0%)
Abdominal discomfort	2 (10.0%)	1 (5.0%)
Cystitis	2 (10.0%)	0 (0.0%)

Note: Values are *n* (%).

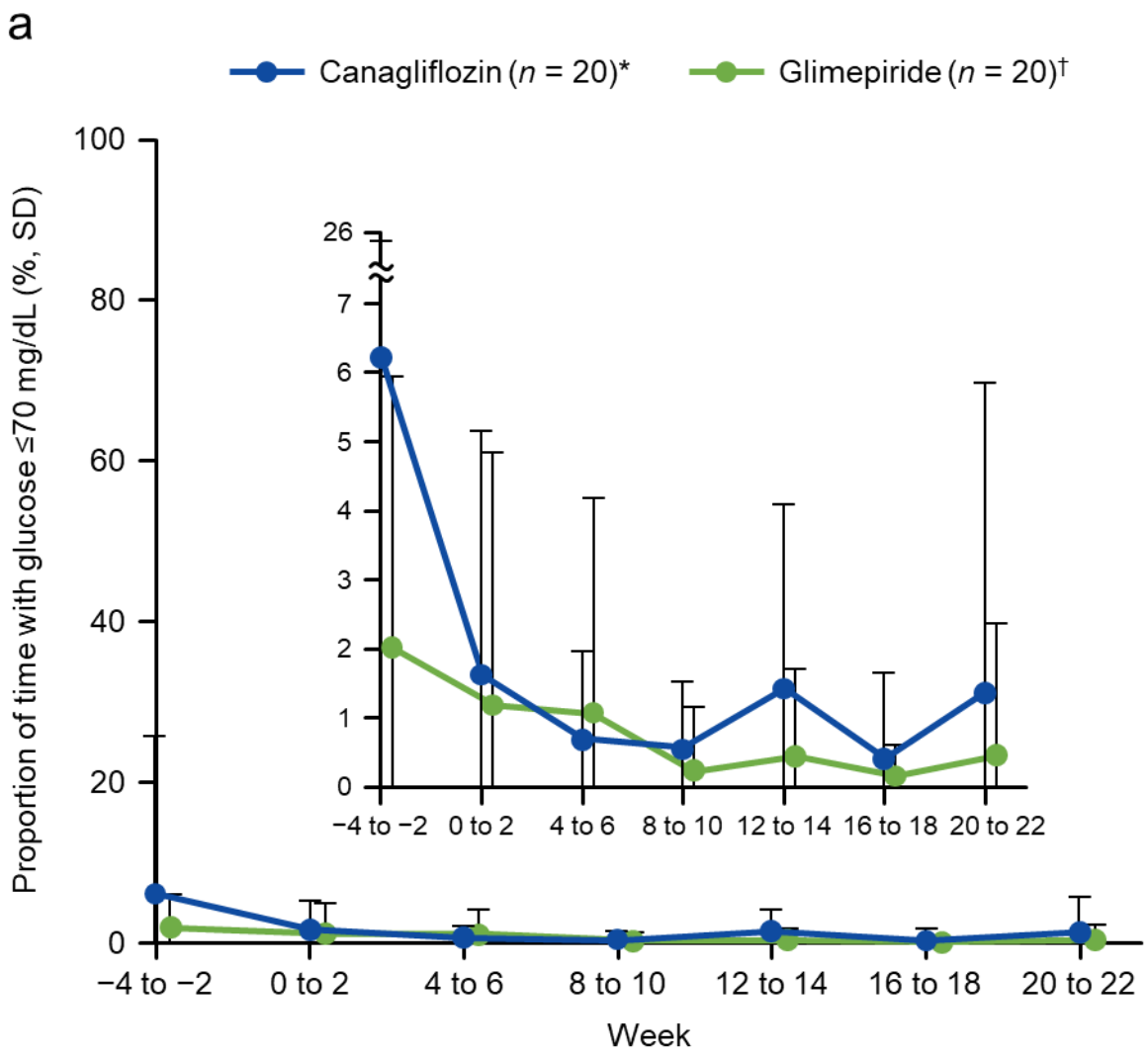
Abbreviations: AE, adverse event; SAE, serious adverse event; ADR, adverse drug reaction.

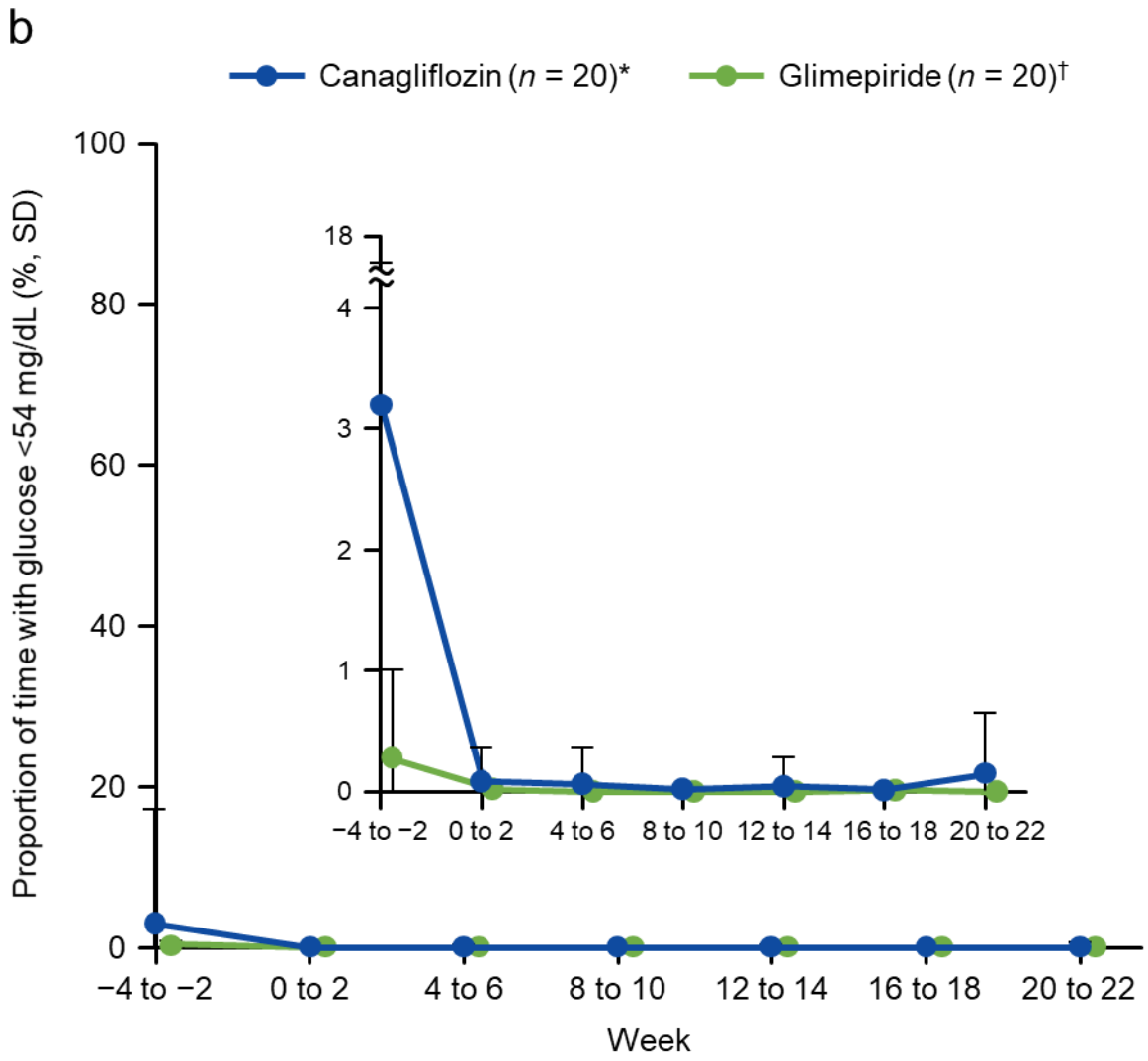
Figure S1 Patient disposition



Note: *One patient was found to meet an exclusion criterion (patients diagnosed with a malignant tumor or patients suspected of a malignant tumor) and was withdrawn from the study.

Figure S2 Nocturnal hypoglycemia. Proportion of time with glucose levels ≤70 mg/dL (≤3.89 mmol/L, **a**) or <54 mg/dL (<3.00 mmol/L, **b**) between 0:00 and 05:59.





Note: The insets show a magnified axis for the proportion of time. Statistical comparisons of the two groups were not performed. Canagliflozin group *n* = 20, glimepiride group *n* = 20, unless otherwise indicated. *Canagliflozin *n* = 18 at week 24; †glimepiride, *n* = 19 at week 12.

Abbreviations: SD, standard deviation.