

Supplementary materials

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Supplemental Table 1. Demographic and other baseline characteristics in the safety analysis set from the double-blind treatment period

Characteristic		All patients N = 232	Saxagliptin N = 117	Placebo N = 115
Sex	Female	90 (38.8%)	45 (38.5%)	45 (39.1%)
	Male	142 (61.2%)	72 (61.5%)	70 (60.9%)
Age (years)	Mean \pm SD	63.6 \pm 10.2	63.5 \pm 10.3	63.7 \pm 10.1
	< 65	118 (50.9%)	61 (52.1%)	57 (49.6%)
	\geq 65	114 (49.1%)	56 (47.9%)	58 (50.4%)
Height (cm)	Mean \pm SD	161.66 \pm 9.38	161.67 \pm 9.15	161.64 \pm 9.65
Weight (kg)	Mean \pm SD	65.43 \pm 13.26	64.28 \pm 10.87	66.61 \pm 15.27
BMI (kg/m ²)	Mean \pm SD	25.00 \pm 4.08	24.60 \pm 3.77	25.41 \pm 4.35
Type of insulin	Long	70 (30.2%)	35 (29.9%)	35 (30.4%)
	Intermediate	1 (0.4%)	1 (0.9%)	0
	Premixed	161 (69.4%)	81 (69.2%)	80 (69.6%)
Duration of diabetes (years)	Mean \pm SD	15.84 \pm 8.99	16.01 \pm 8.26	15.67 \pm 9.71
HbA1c (%)	Mean \pm SD	8.32 \pm 0.65	8.33 \pm 0.68	8.31 \pm 0.61
FPG (mg/dL)	Mean \pm SD	163.7 \pm 38.6	166.3 \pm 40.1	161.0 \pm 37.0
Creatinine clearance (mL/min)	Mean \pm SD	92.46 \pm 37.65	87.18 \pm 28.01	97.83 \pm 44.90
OAD washout period	Yes	107 (46.1%)	55 (47.0%)	52 (45.2%)
Daily insulin dose (IU)	Mean \pm SD	23.29 \pm 8.91	22.86 \pm 8.99	23.73 \pm 8.85
Complications	Any	231 (99.6%)	117 (100.0%)	114 (99.1%)
	Diabetic neuropathy	82 (35.3%)	42 (35.9%)	40 (34.8%)
	Diabetic retinopathy	112 (48.3%)	60 (51.3%)	52 (45.2%)

Diabetic nephropathy	95 (40.9%)	47 (40.2%)	48 (41.7%)
Other	230 (99.1%)	117 (100.0%)	113 (98.3%)

Data set: Safety analysis set during the double-blind period

SD, standard deviation; BMI, body mass index; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; OAD, oral antidiabetic drug

Supplemental Table 2. Subgroup analysis of the changes in HbA1c (%) from baseline to the end of the long-term treatment period

			Saxagliptin→saxagliptin N = 113	Placebo→saxagliptin N = 100
Age				
<65 years	Baseline*	n	61	47
		Mean (95% CI)	8.36 (8.20, 8.53)	8.72 (8.51, 8.93)
	Change from baseline	n	51	45
		Mean (95% CI)	−0.52 (−0.73, −0.32)	−0.74 (−0.95, −0.52)
≥65 years	Baseline*	n	52	53
		Mean (95% CI)	8.25 (8.04, 8.45)	8.19 (8.01, 8.38)
	Change from baseline	n	45	44
		Mean (95% CI)	−0.72 (−0.93, −0.50)	−0.70 (−0.90, −0.50)
HbA1c (%)				
<8.0	Baseline*	n	46	27
		Mean (95% CI)	7.66 (7.60, 7.71)	7.50 (7.38, 7.63)
	Change from baseline	n	37	24
		Mean (95% CI)	−0.47 (−0.66, −0.28)	−0.49 (−0.75, −0.24)
≥8.0	Baseline*	n	67	73
		Mean (95% CI)	8.76 (8.63, 8.88)	8.79 (8.66, 8.91)
	Change from baseline	n	59	65
		Mean (95% CI)	−0.70 (−0.91, −0.50)	−0.80 (−0.97, −0.63)
Insulin type				
Long-acting	Baseline*	n	34	33
		Mean (95% CI)	8.49 (8.24, 8.74)	8.71 (8.46, 8.97)
	Change from baseline	n	29	30
		Mean (95% CI)	−0.59 (−0.89, −0.28)	−0.78 (−1.06, −0.50)
Intermediate-acting	Baseline*	n	1	0
		Mean	8.60	
	Change	n	1	0

	from baseline	Mean (95% CI)	0.80	
Premixed	Baseline*	n	78	67
		Mean (95% CI)	8.23 (8.08, 8.38)	8.31 (8.13, 8.48)
	Change from baseline	n	66	59
		Mean (95% CI)	-0.65 (-0.81, -0.48)	-0.68 (-0.86, -0.51)
FPG at baseline				
<140 mg/dL	Baseline*	n	29	27
		Mean (95% CI)	8.10 (7.85, 8.34)	8.12 (7.80, 8.45)
	Change from baseline	n	23	24
		Mean (95% CI)	-0.58 (-0.82, -0.35)	-0.73 (-0.97, -0.49)
≥140 to <210 mg/dL	Baseline*	n	71	63
		Mean	8.33 (8.18, 8.48)	8.52 (8.34, 8.69)
	Change from baseline	n	68	55
		Mean (95% CI)	-0.64 (-0.83, -0.45)	-0.71 (-0.91, -0.51)
≥210 mg/dL	Baseline*	n	13	10
		Mean (95% CI)	8.65 (8.14, 9.17)	8.81 (8.35, 9.27)
	Change from baseline	n	5	10
		Mean (95% CI)	-0.40 (-1.27, 0.47)	-0.73 (-1.27, -0.19)
Fasting C-peptide				
<1.0 ng/mL	Baseline*	n	64	50
		Mean (95% CI)	8.32 (8.15, 8.49)	8.39 (8.16, 8.63)
	Change from baseline	n	58	43
		Mean(95% CI)	-0.66 (-0.85, -0.47)	-0.61 (-0.79, -0.43)
≥ 1.0 ng/mL	Baseline*	n	49	50
		Mean (95% CI)	8.30 (8.09, 8.50)	8.49 (8.30, 8.67)
	Change from baseline	n	38	46
		Mean (95% CI)	-0.54 (-0.78, -0.31)	-0.82 (-1.04, -0.59)
Daily insulin dose				
<23.06 units [†]	Baseline*	n	56	54
		Mean (95% CI)	8.35 (8.17, 8.53)	8.45 (8.24, 8.65)

≥23.06 units	Change	n	49	48
	from	Mean (95% CI)	-0.76 (-0.98, -0.53)	-0.88 (-1.06, -0.69)
	baseline			
	Baseline*	n	57	46
		Mean (95% CI)	8.27 (8.09, 8.45)	8.43 (8.21, 8.65)
	Change	n	47	41
	from	Mean (95% CI)	-0.46 (-0.64, -0.28)	-0.53 (-0.75, -0.31)
	baseline			

Data set: Full analysis set during the long-term period

HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; CI, confidence interval

*Baseline was defined as the start of saxagliptin: Week 0 in the saxagliptin→saxagliptin group;

Week 16 in the placebo→saxagliptin group.

†Indicates the average daily insulin dose

Supplemental Table 3. Proportion of patients with therapeutic glycemic response

n (%)	Saxagliptin N = 113	Placebo N = 115
Double-blind period		
Age <65		
HbA1c <7.0% at Baseline	0/61 (0.0%)	0/57 (0.0%)
HbA1c <7.0% at Week 16	10/57 (17.5%)	0/49 (0.0%)
HbA1c <7.0% with no hypoglycemic event [†] during 4 weeks before Week 16	9/57 (15.8%)	0/49 (0.0%)
Age ≥65		
HbA1c <7.0% at Baseline	0/52 (0.0%)	0/58 (0.0%)
HbA1c <7.0% at Week 16	12/48 (25.0%)	1/55 (1.8%)
HbA1c <7.0% with no hypoglycemic event [†] during 4 weeks before Week 16	12/48 (25.0%)	1/55 (1.8%)
65 ≤ Age < 75		
HbA1c <7.5% at Baseline	3/39 (7.7%)	2/40 (5.0%)
HbA1c <7.5% at Week 16	24/37 (64.9%)	5/40 (12.5%)
HbA1c <7.5% with no hypoglycemic event [†] during 4 weeks before Week 16	23/37 (62.2%)	5/40 (12.5%)
Age ≥75		
HbA1c <8.0% at Baseline	8/13 (61.5%)	7/18 (38.9%)
HbA1c <8.0% at Week 16	10/11 (90.9%)	8/15 (53.3%)
HbA1c <8.0% with no hypoglycemic event [†] during 4 weeks before Week 16	10/11 (90.9%)	7/15 (46.7%)

event[†] during 4 weeks before Week 16

	Saxagliptin→saxagliptin N = 113	Placebo→saxagliptin N = 100
Double-blind period and Open-label extension period		
Age <65		
HbA1c <7.0% at Baseline*	0/61 (0.0%)	0/47 (0.0%)
HbA1c <7.0% at Week 52	7/51 (13.7%)	5/45 (11.1%)
HbA1c <7.0% with no hypoglycemic event [†] during 4 weeks before Week 52	7/51 (13.7%)	4/45 (8.9%)
Age ≥65		
HbA1c <7.0% at Baseline*	0/52 (0.0%)	1/53 (1.9%)
HbA1c <7.0% at Week 52	9/45 (20.0%)	9/44 (20.5%)
HbA1c <7.0% with no hypoglycemic event [†] during 4 weeks before Week 52	8/45 (17.8%)	9/44 (20.5%)
65 ≤ Age < 75		
HbA1c <7.5% at Baseline*	3/39 (7.7%)	5/39 (12.8%)
HbA1c <7.5% at Week 52	22/35 (62.9%)	19/33 (57.6%)
HbA1c <7.5% with no hypoglycemic event [†] during 4 weeks before Week 52	21/35 (60.0%)	19/33 (57.6%)
Age ≥75		
HbA1c <8.0% at Baseline*	8/13 (61.5%)	8/14 (57.1%)
HbA1c <8.0% at Week 52	7/10 (70.0%)	7/11 (63.6%)

HbA1c <8.0% with no hypoglycemic event [†] during 4 weeks before Week 52	7/10 (70.0%)	6/11 (54.5%)
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Data set: Full analysis set during the double-blind period and full analysis set during the long-term period

Data are shown as n (%)

HbA1c, hemoglobin A1c

*Baseline was defined as the start of saxagliptin: Week 0 in the saxagliptin→saxagliptin group; Week 16 in the placebo→saxagliptin group.

Supplemental Table 4. Meal tolerance test-related variables

Variable	Saxagliptin	Placebo	Difference vs placebo [†] (95% CI)
	N =113	N =115	
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120-min PPG (mg/dL)			
n	103	102	
Baseline, mean (SE)	263.3 (5.73)	250.3 (5.76)	
Week 16, mean (SE)	215.8 (4.69)	256.4 (5.66)	
Adjusted change (95% CI)	-7.6 (-38.4, 23.2)	38.2 (6.5, 69.9)	-45.8 (-58.5, -33.0)
PPG AUC _{0-120 min} (mg·min/dL)			
n	103	102	
Baseline, mean (SE)	28,025.5 (506.95)	26,894.7 (492.33)	
Week 16, mean (SE)	23,056.6 (442.72)	27,439.0 (494.66)	
Adjusted change (95% CI)	-148.2 (-2899.5, 2603.2)	47,63.0 (1924.4, 7601.6)	-4911.1 (-6049.7, -3772.6)
120-min postprandial C-peptide (ng/mL)			
n	103	102	
Baseline, mean (SE)	2.47 (0.108)	2.51 (0.126)	

Week 16, mean (SE)	2.66 (0.129)	2.60 (0.123)	
Adjusted change (95% CI)	0.27 (-0.29, 0.82)	0.18 (-0.40, 0.75)	0.09 (-0.14, 0.32)
C-peptide AUC _{0-120 min} (ng·min/mL)			
n	103	102	
Baseline, mean (SE)	223.86 (9.777)	232.93 (11.606)	
Week 16, mean (SE)	231.32 (10.661)	242.79 (11.857)	
Adjusted change (95% CI)	23.12 (-20.27, 66.50)	26.92 (-17.66, 71.50)	-3.80 (-21.59, 13.98)
120-min postprandial glucagon (pg/mL)			
n	103	102	
Baseline, mean (SE)	130.3 (2.41)	130.6 (2.03)	
Week 16, mean (SE)	121.1 (2.33)	122.8 (2.30)	
Adjusted change (95% CI)	-14.5 (-27.4, -1.7)	-13.0 (-26.2, 0.3)	-1.6 (-6.9, 3.7)
Glucagon AUC _{0-120 min} (pg·min/mL)			
n	103	102	
Baseline, mean (SE)	16,556.2 (291.49)	16,827.5 (288.21)	
Week 16, mean (SE)	14,865.3 (254.26)	15,536.0 (302.00)	
Adjusted change (95% CI)	-2497.2 (-3952.8, -1041.6)	-2016.2 (-3514.5, -517.9)	-481.1 (-1080.0, 117.9)

Data set: Full analysis set during the double-blind period

PPG, postprandial plasma glucose; CI, confidence interval; SE, standard error; $AUC_{0-120 \text{ min}}$, area under the concentration–time curve from 0 to 120 min

[†]Difference vs Placebo: Adjusted change from baseline for saxagliptin — Adjusted change from baseline for placebo

Supplemental Table 5. Meal tolerance test-related variables by age.

Variable		Saxagliptin	Placebo	Difference vs placebo [†] (95% CI)
Age <65 years		N = 61	N = 57	
Preprandial plasma glucose (mg/dL)				
Baseline	n	61	57	
	Mean (95% CI)	172.8 (161.8, 183.8)	166.8 (157.4, 176.3)	
Week 16	n	55	48	
	Mean (95% CI)	151.4 (142.0, 160.9)	166.2 (155.9, 176.6)	-24.8 (-40.0, -9.6)
30-min PPG (mg/dL)				
Baseline	n	61	57	
	Mean (95% CI)	222.5 (211.7, 233.4)	215.5 (203.8, 227.3)	
Week 16	n	55	48	
	Mean (95% CI)	187.5 (176.8, 198.1)	214.7 (202.0, 227.5)	-37.6 (-55.8, -19.3)
60-min PPG (mg/dL)				
Baseline	n	61	57	
	Mean (95% CI)	262.3 (247.6, 276.9)	254.7 (240.5, 268.9)	
Week 16	n	55	48	

	Mean (95% CI)	216.8 (203.1, 230.6)	255.3 (240.1, 270.6)	-48.8 (-70.1, -27.5)
120-min PPG (mg/dL)				
Baseline	n	61	57	
	Mean (95% CI)	266.7 (249.5, 284.0)	249.4 (234.1, 264.7)	
Week 16	n	55	48	
	Mean (95% CI)	224.2 (209.2, 239.2)	259.5 (240.7, 278.3)	-56.1 (-82.3, -29.9)
PPG AUC _{0-120 min} (mg·min/dL)				
Baseline	n	61	57	
	Mean (95% CI)	29,072.2 (27,610.7, 30,533.7)	27,911.6 (26,474.4, 29,348.7)	
Week 16	n	55	48	
	Mean (95% CI)	24,378.8 (23012.5, 25,745.1)	28,209.7 (26,605.8, 29,813.6)	-5377.6 (-7665.6, -3089.7)
Preprandial C-peptide (ng/mL)				
Baseline	n	61	57	
	Mean (95% CI)	1.07 (0.92, 1.22)	1.13 (1.00, 1.27)	
Week 16	n	55	48	
	Mean (95% CI)	1.03 (0.88, 1.19)	1.23 (1.06, 1.39)	-0.10 (-0.26, 0.05)
30-min postprandial C-peptide (ng/mL)				

Baseline	n	61	57	
	Mean (95% CI)	1.66 (1.45, 1.87)	1.81 (1.60, 2.01)	
Week 16	n	55	48	
	Mean (95% CI)	1.56 (1.35, 1.77)	1.91 (1.66, 2.15)	-0.10 (-0.32, 0.12)

60-min postprandial C-peptide

(ng/mL)

Baseline	n	61	57	
	Mean (95% CI)	2.05 (1.82, 2.29)	2.42 (2.15, 2.68)	
Week 16	n	55	48	
	Mean (95% CI)	2.01 (1.76, 2.26)	2.55 (2.24, 2.86)	-0.06 (-0.34, 0.22)

120-min postprandial C-peptide

(ng/mL)

Baseline	n	61	57	
	Mean (95% CI)	2.49 (2.20, 2.78)	2.78 (2.43, 3.13)	
Week 16	n	55	48	
	Mean (95% CI)	2.57 (2.21, 2.93)	2.87 (2.52, 3.22)	0.08 (-0.30, 0.46)

C-peptide AUC_{0-120 min} (ng·min/mL)

Baseline	n	61	57	
	Mean (95% CI)	232.89 (206.11, 259.68)	263.24 (234.75, 291.72)	
Week 16	n	55	48	

	Mean (95% CI)	229.99 (201.52, 258.46)	276.63 (244.27, 308.98)	-5.04 (-34.34, 24.26)
Preprandial glucagon (pg/mL)				
Baseline	n	61	57	
	Mean (95% CI)	120.0 (114.9, 125.2)	123.9 (119.0, 128.8)	
Week 16	n	55	48	
	Mean (95%CI)	114.8 (110.7, 118.9)	117.0 (111.4, 122.6)	2.4 (-4.2, 9.0)
30-min postprandial glucagon (pg/mL)				
Baseline	n	61	57	
	Mean (95% CI)	145.3 (138.1, 152.6)	154.6 (145.1, 164.0)	
Week 16	n	55	48	
	Mean (95% CI)	124.3 (118.3, 130.3)	142.9 (133.7, 152.1)	-7.3 (-18.1, 3.5)
60-min postprandial glucagon (pg/mL)				
Baseline	n	61	57	
	Mean (95% CI)	141.9 (134.3, 149.4)	152.2 (142.6, 161.8)	
Week 16	n	55	48	
	Mean (95% CI)	128.1 (121.0, 135.2)	139.2 (129.1, 149.3)	0.7 (-9.9, 11.4)
120-min postprandial glucagon (pg/mL)				

Baseline	n	61	57	
	Mean (95% CI)	129.6 (123.1, 136.1)	132.0 (126.0, 138.0)	
Week 16	n	55	48	
	Mean (95% CI)	120.1 (113.8, 126.5)	123.7 (116.8, 130.5)	-0.6 (-9.4, 8.3)
Glucagon AUC _{0-120 min} (pg·min/mL)				
Baseline	n	61	57	
	Mean (95% CI)	16,432.9 (15661.2, 17,204.5)	17,302.6 (16,401.9, 18,203.4)	
Week 16	n	55	48	
	Mean (95% CI)	14,819.2 (14133.2, 15,505.2)	16,016.9 (15076.3, 16,957.4)	-167.9 (-1187.4, 851.5)
Age ≥65 years		N = 52	N = 58	
Preprandial plasma glucose (mg/dL)				
Baseline	n	52	58	
	Mean (95% CI)	153.6 (144.5, 162.8)	152.8 (143.1, 162.5)	
Week 16	n	48	54	
	Mean (95% CI)	133.4 (126.2, 140.5)	157.2 (146.8, 167.5)	-24.5 (-36.9, -12.1)
30-min PPG (mg/dL)				

Baseline	n	52	58	
	Mean (95% CI)	199.8 (188.2, 211.4)	199.1 (187.7, 210.5)	
Week 16	n	48	54	
	Mean (95% CI)	166.0 (158.6, 173.4)	201.2 (190.7, 211.7)	-35.2 (-49.7, -20.7)
60-min PPG (mg/dL)				
Baseline	n	52	58	
	Mean (95% CI)	241.7 (229.8, 253.6)	235.1 (222.7, 247.5)	
Week 16	n	48	54	
	Mean (95% CI)	186.1 (176.4, 195.9)	238.9 (227.9, 249.9)	-60.5 (-76.7, -44.4)
120-min PPG (mg/dL)				
Baseline	n	52	58	
	Mean (95% CI)	261.5 (248.4, 274.6)	254.8 (238.8, 270.7)	
Week 16	n	48	54	
	Mean (95% CI)	206.1 (196.1, 216.2)	253.6 (240.0, 267.2)	-53.4 (-72.0, -34.8)
PPG AUC _{0-120 min} (mg·min/dL)				
Baseline	n	52	58	
	Mean (95% CI)	27,020.2 (25,813.7, 28,226.7)	26,488.2 (25,141.3, 27,835.1)	
Week 16	n	48	54	
	Mean (95% CI)	21,541.6 (20,619.8, 22,463.4)	26,753.9 (25,548.9, 27,958.9)	-5749.5 (-7460.7, -4038.3)

		22,463.3)	27,958.9)	-4038.3)
Preprandial C-peptide (ng/mL)				
Baseline	n	52	58	
	Mean (95% CI)	0.95 (0.80, 1.10)	0.96 (0.79, 1.13)	
Week 16	n	48	54	
	Mean (95% CI)	1.01 (0.82, 1.20)	0.95 (0.77, 1.14)	0.05 (-0.10, 0.19)
30-min postprandial C-peptide (ng/mL)				
Baseline	n	52	58	
	Mean (95% CI)	1.47 (1.28, 1.65)	1.43 (1.17, 1.68)	
Week 16	n	48	54	
	Mean (95% CI)	1.56 (1.32, 1.81)	1.46 (1.20, 1.73)	0.04 (-0.14, 0.22)
60-min postprandial C-peptide (ng/mL)				
Baseline	n	52	58	
	Mean (95% CI)	1.96 (1.72, 2.20)	1.79 (1.51, 2.06)	
Week 16	n	48	54	
	Mean (95% CI)	1.96 (1.68, 2.25)	1.86 (1.57, 2.16)	-0.10 (-0.31, 0.10)
120-min postprandial C-peptide				

(ng/mL)

Baseline	n	52	58	
	Mean (95% CI)	2.52 (2.24, 2.81)	2.27 (1.97, 2.57)	
Week 16	n	48	54	
	Mean (95% CI)	2.75 (2.37, 3.13)	2.35 (2.02, 2.69)	0.12 (-0.16, 0.40)

C-peptide AUC_{0-120 min} (ng·min/mL)

Baseline	n	52	58	
	Mean (95% CI)	222.09 (196.41, 247.76)	205.66 (175.34, 235.97)	
Week 16	n	48	54	
	Mean (95% CI)	232.84 (200.17, 265.51)	212.72 (180.01, 245.43)	0.78 (-20.73, 22.29)

Preprandial glucagon (pg/mL)

Baseline	n	52	58	
	Mean (95% CI)	124.3 (118.0, 130.5)	120.9 (116.4, 125.3)	
Week 16	n	48	54	
	Mean (95% CI)	118.1 (111.8, 124.5)	112.7 (107.4, 118.0)	1.6 (-6.4, 9.7)

30-min postprandial glucagon

(pg/mL)

Baseline	n	52	58	
	Mean (95% CI)	145.5 (138.2, 152.7)	143.7 (138.3, 149.1)	
Week 16	n	48	54	

	Mean (95% CI)	127.4 (120.5, 134.3)	132.0 (124.8, 139.2)	-7.6 (-16.2, 1.0)
60-min postprandial glucagon				
(pg/mL)				
Baseline	n	52	58	
	Mean (95% CI)	145.1 (138.0, 152.3)	140.9 (135.5, 146.4)	
Week 16	n	48	54	
	Mean (95% CI)	125.8 (119.0, 132.5)	128.8 (121.4, 136.2)	-8.3 (-16.8, 0.3)
120-min postprandial glucagon				
(pg/mL)				
Baseline	n	52	58	
	Mean (95%CI)	131.5 (125.3, 137.6)	129.8 (125.4, 134.2)	
Week 16	n	48	54	
	Mean (95% CI)	122.2 (115.2, 129.2)	122.1 (115.8, 128.4)	-2.3 (-10.0, 5.5)
Glucagon AUC _{0-120 min} (pg·min/mL)				
Baseline	n	52	58	
	Mean (95% CI)	16,702.5 (15,938.4, 17,466.6)	16,359.8 (15,832.5, 16,887.2)	
Week 16	n	48	54	
	Mean (95% CI)	14,918.1 (14,147.2, 15,689.0)	15,108.6 (14,335.2, 15,882.0)	-643.5 (-1523.1, 236.1)

Data set: Full analysis set during the double-blind period

PPG, postprandial plasma glucose; CI, confidence interval; SE, standard error; $AUC_{0-120 \text{ min}}$, area under the concentration–time curve from 0 to 120 min

[†]Difference vs Placebo: Mean change for saxagliptin – Mean change for placebo

Supplemental Table 6. Meal tolerance test-related variables by insulin type.

Variable		Saxagliptin	Placebo	Difference vs placebo [†] (95% CI)
Premixed/Intermediate-acting insulin		N = 79	N = 80	
Preprandial plasma glucose (mg/dL)				
Baseline	n	79	80	
	Mean (95% CI)	163.9 (156.4, 171.5)	166.1 (158.1, 174.1)	
Week 16	n	72	68	
	Mean (95% CI)	144.7 (138.0, 151.4)	164.4 (155.3, 173.5)	-21.0 (-32.9, -9.0)
30-min PPG (mg/dL)				
Baseline	n	79	80	
	Mean (95% CI)	208.5 (198.6, 218.5)	210.0 (199.7, 220.3)	
Week 16	n	72	68	
	Mean (95% CI)	175.5 (167.5, 183.5)	206.1 (196.5, 215.6)	-31.4 (-45.8, -17.0)
60-min PPG (mg/dL)				
Baseline	n	79	80	
	Mean (95% CI)	241.0 (229.4, 252.5)	241.6 (229.9, 253.3)	
Week 16	n	72	68	
	Mean (95% CI)	193.1 (182.6, 203.6)	238.1 (226.9, 249.4)	-48.8 (-65.7, -32.0)
120-min PPG (mg/dL)				

Baseline	n	79	80	
	Mean (95% CI)	250.4 (238.3, 262.5)	251.9 (238.3, 265.5)	
Week 16	n	72	68	
	Mean (95% CI)	202.4 (192.4, 212.5)	251.4 (236.9, 266.0)	-50.6 (-70.9, -30.2)
PPG AUC _{0-120 min} (mg·min/dL)				
Baseline	n	79	80	
	Mean (95% CI)	27,071.2 (25,936.5, 28,205.9)	27,221.4 (26,001.1, 28,441.8)	
Week 16	n	72	68	
	Mean (95% CI)	22,197.9 (21,195.5, 23,200.4)	26,908.0 (25,700.1, 28,115.9)	-4969.8 (-6780.8, -3158.9)
Preprandial C-peptide (ng/mL)				
Baseline	n	79	80	
	Mean (95% CI)	1.05 (0.93, 1.18)	1.05 (0.92, 1.18)	
Week 16	n	72	68	
	Mean (95% CI)	1.08 (0.93, 1.23)	1.07 (0.91, 1.23)	-0.02 (-0.14, 0.10)
30-min postprandial C-peptide (ng/mL)				
Baseline	n	79	80	
	Mean (95% CI)	1.61 (1.44, 1.79)	1.53 (1.34, 1.73)	
Week 16	n	72	68	

	Mean (95% CI)	1.65 (1.46, 1.84)	1.58 (1.35, 1.81)	-0.01 (-0.18, 0.15)
60-min postprandial C-peptide (ng/mL)				
Baseline	n	79	80	
	Mean (95% CI)	2.06 (1.86, 2.26)	1.93 (1.71, 2.15)	
Week 16	n	72	68	
	Mean (95% CI)	2.03 (1.81, 2.25)	1.98 (1.73, 2.24)	-0.11 (-0.30, 0.09)
120-min postprandial C-peptide (ng/mL)				
Baseline	n	79	80	
	Mean (95% CI)	2.43 (2.19, 2.67)	2.28 (2.02, 2.54)	
Week 16	n	72	68	
	Mean (95% CI)	2.54 (2.25, 2.83)	2.35 (2.06, 2.65)	0.00 (-0.25, 0.25)
C-peptide AUC _{0-120 min} (ng·min/mL)				
Baseline	n	79	80	
	Mean (95% CI)	229.77 (207.33, 252.20)	217.29 (192.89, 241.69)	
Week 16	n	72	68	
	Mean (95% CI)	233.25 (208.30, 258.20)	223.30 (194.75, 251.85)	-5.38 (-25.14, 14.38)
Preprandial glucagon (pg/mL)				
Baseline	n	79	80	

	Mean (95% CI)	123.6 (118.6, 128.6)	123.0 (119.4, 126.6)	
Week 16	n	72	68	
	Mean (95% CI)	117.4 (112.8, 122.0)	115.7 (111.3, 120.1)	0.7 (−5.6, 7.0)
30-min postprandial glucagon (pg/mL)				
Baseline	n	79	80	
	Mean (95% CI)	145.4 (139.1, 151.6)	146.7 (141.0, 152.4)	
Week 16	n	72	68	
	Mean (95% CI)	126.5 (120.8, 132.2)	134.8 (128.3, 141.3)	−7.3 (−15.5, 0.8)
60-min postprandial glucagon (pg/mL)				
Baseline	n	79	80	
	Mean (95% CI)	143.7 (137.4, 150.0)	142.8 (137.5, 148.0)	
Week 16	n	72	68	
	Mean (95% CI)	128.3 (122.1, 134.5)	131.0 (125.0, 137.1)	−5.0 (−12.9, 3.0)
120-min postprandial glucagon (pg/mL)				
Baseline	n	79	80	
	Mean (95% CI)	130.7 (125.2, 136.1)	130.5 (126.7, 134.3)	
Week 16	n	72	68	
	Mean (95% CI)	123.2 (117.2, 129.3)	123.4 (118.2, 128.7)	−0.8 (−7.6, 6.0)
Glucagon AUC _{0–120 min} (pg·min/mL)				

Baseline	n	79	80	
	Mean (95% CI)	16,601.6 (15,938.8, 17,264.4)	16,583.1 (16,075.0, 17,091.2)	
Week 16	n	72	68	
	Mean (95% CI)	15,024.6 (14,373.7, 15,675.5))	15,378.5 (14,738.2, 16,018.9)	-457.5 (-1240.2, 325.2)
Long-acting insulin		N = 34	N = 35	
Preprandial plasma glucose (mg/dL)				
Baseline	n	34	35	
	Mean (95% CI)	164.1 (146.0, 182.1)	145.3 (133.3, 157.2)	
Week 16	n	31	34	
	Mean (95% CI)	139.2 (125.1, 153.2)	155.5 (143.3, 167.7)	-32.5 (-49.4, -15.6)
30-min PPG (mg/dL)				
Baseline	n	34	35	
	Mean (95% CI)	220.3 (206.2, 234.5)	200.9 (187.0, 214.7)	
Week 16	n	31	34	
	Mean (95% CI)	182.0 (168.1, 195.8)	210.6 (194.6, 226.5)	-47.0 (-66.4, -27.6)
60-min PPG (mg/dL)				
Baseline	n	34	35	

	Mean (95% CI)	280.3 (266.0, 294.6)	252.2 (235.6, 268.8)	
Week 16	n	31	34	
	Mean (95% CI)	224.5 (208.8, 240.1)	263.7 (248.4, 278.9)	-65.2 (-86.4, -44.1)
120-min PPG (mg/dL)				
Baseline	n	34	35	
	Mean (95% CI)	296.7 (276.6, 316.7)	252.6 (233.8, 271.4)	
Week 16	n	31	34	
	Mean (95% CI)	246.8 (230.8, 262.8)	266.2 (248.7, 283.7)	-59.3 (-85.6, -33.0)
PPG AUC _{0-120 min} (mg·min/dL)				
Baseline	n	34	35	
	Mean (95% CI)	30,583.2 (28,936.4, 32,230.0)	27,130.3 (25,442.2, 28,818.4)	
Week 16	n	31	34	
	Mean (95% CI)	25,051.0 (23,423.3, 26,678.6)	28,500.9 (26,788.6, 30,213.2)	-6613.2 (-8838.7, -4387.6)
Preprandial C-peptide (ng/mL)				
Baseline	n	34	35	
	Mean (95% CI)	0.93 (0.73, 1.12)	1.03 (0.83, 1.23)	
Week 16	n	31	34	
	Mean (95% CI)	0.89 (0.69, 1.09)	1.11 (0.90, 1.32)	-0.05 (-0.26, 0.17)

30-min postprandial C-peptide (ng/mL)

Baseline	n	34	35	
	Mean (95% CI)	1.47 (1.22, 1.72)	1.80 (1.49, 2.11)	
Week 16	n	31	34	
	Mean (95% CI)	1.35 (1.08, 1.62)	1.86 (1.55, 2.16)	-0.11 (-0.38, 0.16)

60-min postprandial C-peptide (ng/mL)

Baseline	n	34	35	
	Mean (95% CI)	1.90 (1.59, 2.21)	2.48 (2.09, 2.87)	
Week 16	n	31	34	
	Mean (95% CI)	1.90 (1.53, 2.26)	2.60 (2.19, 3.00)	-0.03 (-0.39, 0.33)

120-min postprandial C-peptide (ng/mL)

Baseline	n	34	35	
	Mean (95% CI)	2.67 (2.30, 3.05)	3.06 (2.61, 3.51)	
Week 16	n	31	34	
	Mean (95% CI)	2.92 (2.38, 3.46)	3.09 (2.70, 3.47)	0.31 (-0.20, 0.82)

C-peptide AUC_{0-120 min} (ng·min/mL)

		34	35	
Baseline	n	223.63 (189.83,	272.83 (232.29,	
		257.44)	313.37)	
	Mean (95% CI)	31	34	
Week 16	n	226.84 (184.86,	281.78 (241.54,	

		268.82)	322.02)	
	Mean (95% CI)			3.88 (-34.76, 42.53)
Preprandial glucagon (pg/mL)				
Baseline	n	34	35	
	Mean (95% CI)	118.2 (111.9, 124.6)	121.0 (113.8, 128.2)	
Week 16	n	31	34	
	Mean (95% CI)	113.9 (107.9, 119.8)	112.9 (105.4, 120.5)	5.3 (-3.9, 14.5)
30-min postprandial glucagon (pg/mL)				
Baseline	n	34	35	
	Mean (95% CI)	145.5 (136.4, 154.6)	154.6 (142.0, 167.1)	
Week 16	n	31	34	
	Mean (95% CI)	124.0 (116.6, 131.4)	141.8 (130.1, 153.5)	-8.3 (-21.2, 4.6)
60-min postprandial glucagon (pg/mL)				
Baseline	n	34	35	
	Mean (95% CI)	142.5 (133.1, 151.9)	155.1 (141.6, 168.6)	
Week 16	n	31	34	
	Mean (95% CI)	124.1 (116.6, 131.6)	139.0 (124.7, 153.3)	-1.1 (-14.4, 12.3)
120-min postprandial glucagon (pg/mL)				
Baseline	n	34	35	
	Mean (95% CI)	130.0 (121.9, 138.2)	131.8 (123.2, 140.4)	

Week 16	n	31	34	
	Mean (95% CI)	116.1 (109.6, 122.6)	121.6 (112.5, 130.7)	-3.1 (-14.2, 8.1)
Glucagon AUC _{0-120 min} (pg·min/mL)				
Baseline	n	34	35	
	Mean (95% CI)	16,453.2 (15498.0, 17,408.5)	17,385.0 (16,104.1, 18,665.9)	
Week 16	n	31	34	
	Mean (95% CI)	14,495.3 (13,736.6, 15,254.1)	15,851.0 (14,540.5, 17,161.6)	-309.9 (-1598.1, 978.3)

Data set: Full analysis set during the double-blind period

PPG, postprandial plasma glucose; CI, confidence interval; SE, standard error; AUC_{0-120 min}, area under the concentration–time curve from 0 to 120 min

[†]Difference vs Placebo: Mean change for saxagliptin – Mean change for placebo

Supplemental Table 7. Subgroup analysis of clinical efficacy variables during the double-blind and open-label extension periods by age

Variable (unit)	Study period		Saxagliptin	Placebo	Difference vs placebo [†] (95% CI)
			N = 113	n = 115	
Double-blind period					
FPG (mg/dL)					
Age <65 years	Baseline	N	61	57	
		Mean (95% CI)	174.9 (164.1, 185.7)	167.8 (158.1, 177.6)	
	Week 16	N	57	49	
		Mean (95% CI)	152.5 (143.1, 161.9)	167.3 (156.8, 177.8)	−26.6 (−41.8, −11.4)
Age ≥65 years	Baseline	N	52	58	
		Mean (95% CI)	154.0 (145.2, 162.8)	154.3 (144.7, 163.8)	
	Week 16	n	48	55	
		Mean (95% CI)	134.4 (126.9, 142.0)	157.5 (147.8, 167.3)	−22.3 (−34.8, −9.8)
Fasting C-peptide (ng/mL)					
Age <65 years	Baseline	n	61	57	
		Mean (95% CI)	1.08 (0.92, 1.24)	1.16 (1.02, 1.30)	
	Week 16	n	57	49	
		Mean (95% CI)	0.97 (0.83, 1.11)	1.19 (1.03, 1.35)	−0.14 (−0.30, 0.02)
Age ≥65 years	Baseline	n	52	58	
		Mean (95% CI)	0.96 (0.81, 1.11)	0.95 (0.79, 1.11)	
	Week 16	n	48	55	
		Mean (95% CI)	1.02 (0.83, 1.20)	0.92 (0.76, 1.07)	0.07 (−0.06, 0.21)

Fasting glucagon (pg/mL)					
Age <65 years	Baseline	n	61	57	
		Mean (95% CI)	124.0 (118.3, 129.8)	125.4 (119.6, 131.2)	
	Week 16	n	57	49	
		Mean (95% CI)	114.6 (110.0, 119.1)	116.4 (110.5, 122.4)	−0.4 (−8.6, 7.7)
Age ≥65 years	Baseline	n	52	58	
		Mean (95% CI)	125.2 (118.9, 131.5)	122.5 (118.0, 126.9)	
	Week 16	n	48	55	
		Mean (95% CI)	118.0 (111.6, 124.4)	114.4 (109.0, 119.8)	0.0 (−7.7, 7.7)
1,5-AG (µg/mL)					
Age <65 years	Baseline	n	61	57	
		Mean (95% CI)	3.64 (3.03, 4.25)	3.67 (3.00, 4.34)	
	Week 16	n	57	49	
		Mean (95% CI)	6.66 (5.16, 8.16)	3.37 (2.69, 4.05)	3.37 (2.16, 4.58)
Age ≥65 years	Baseline	n	52	58	
		Mean (95% CI)	4.58 (3.79, 5.36)	4.18 (3.53, 4.83)	
	Week 16	n	48	55	
		Mean (95% CI)	7.54 (6.32, 8.75)	4.00 (3.26, 4.74)	3.04 (2.28, 3.81)
			Saxagliptin→saxagliptin	Placebo→saxagliptin	
			N = 113	N = 100	
Double-blind period and					
Open-label extension period					
FPG (mg/dL)					
Age <65 years	Baseline*	n	61	47	
		Mean (95% CI)	174.9 (164.1, 185.7)	167.7 (156.7, 178.7)	
	Week 52	n	51	44	

Fasting C-peptide (ng/mL)	Age ≥65 years	Baseline*	Mean (95% CI)	148.3 (137.5, 159.0)	155.8 (144.4, 167.2)
			n	52	53
	Week 52	Baseline*	Mean (95% CI)	154.0 (145.2, 162.8)	156.7 (146.7, 166.7)
			n	45	44
		Week 52	Mean (95% CI)	145.6 (134.1, 157.0)	143.1 (133.1, 153.1)
			n	45	44
Fasting glucagon (pg/mL)	Age <65 years	Baseline*	n	61	47
			Mean (95% CI)	1.08 (0.92, 1.24)	1.18 (1.02, 1.35)
	Week 52	Baseline*	n	51	44
			Mean (95% CI)	1.03 (0.85, 1.21)	1.29 (1.08, 1.50)
		Week 52	n	52	53
			Mean (95% CI)	0.96 (0.81, 1.11)	0.90 (0.74, 1.06)
1,5-AG (μg/mL)	Age ≥65 years	Baseline*	n	52	53
			Mean (95% CI)	0.91 (0.77, 1.04)	0.90 (0.73, 1.08)
	Week 52	Baseline*	n	61	47
			Mean (95% CI)	124.0 (118.3, 129.8)	116.1 (109.9, 122.4)
		Week 52	n	51	44
			Mean (95% CI)	108.8 (103.5, 114.0)	114.9 (106.5, 123.3)
1,5-AG (μg/mL)	Age <65 years	Baseline*	n	52	53
			Mean (95% CI)	125.2 (118.9, 131.5)	114.9 (109.3, 120.4)
	Week 52	Baseline*	n	45	44
			Mean (95% CI)	119.3 (110.7, 127.9)	105.5 (99.4, 111.7)
		Week 52	n	45	44
			Mean (95% CI)	3.64 (3.03, 4.25)	3.30 (2.64, 3.97)

Age ≥65 years	Baseline*	Mean (95% CI)	6.00 (4.73, 7.28)	5.75 (4.36, 7.14)
		n	52	53
	Week 52	Mean (95% CI)	4.58 (3.79, 5.36)	3.76 (3.19, 4.33)
		n	45	44
		Mean (95% CI)	6.49 (5.44, 7.55)	6.11 (5.11, 7.11)

Data set: Full analysis set during the double-blind period and full analysis set during the long-term period

FPG, fasting plasma glucose; 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval

*Baseline was defined as the start of saxagliptin: Week 0 in the saxagliptin→saxagliptin group; Week 16 in the placebo→saxagliptin group.

†Difference vs Placebo: Mean change for saxagliptin — Mean change for placebo

Supplemental Table 8. Subgroup analysis of the incidence of hypoglycemia and blood glucose decreased by insulin type

	TEAEs		Drug-related TEAEs	
	Saxagliptin	Placebo	Saxagliptin	Placebo
Premixed/Intermediate-acting	N = 82	N = 80	N = 82	N = 80
Long-acting	N = 35	N = 35	N = 35	N = 35
n (%)				
Double-blind period				
TEAE by preferred term				
Hypoglycemia				
Premixed/Intermediate-acting	18 (22.0%)	15 (18.8%)	13 (15.9%)	13 (16.3%)
Long-acting	6 (17.1%)	2 (5.7%)	5 (14.3%)	2 (5.7%)
Blood glucose decreased				
Premixed/Intermediate-acting	2 (2.4%)	0	1 (1.2%)	0
Long-acting	0	0	0	0
	Saxagliptin→	Placebo→	Saxagliptin→	Placebo→
	saxagliptin	saxagliptin	saxagliptin	saxagliptin
Premixed/Intermediate-acting	N = 82	N = 69	N = 82	N = 69
Long-acting	N = 35	N = 34	N = 35	N = 34
n (%)				
Double-blind period and				
Open-label extension period*				
TEAE by preferred term				
Hypoglycemia				
Premixed/Intermediate-acting	26 (31.7%)	16 (23.2%)	21 (25.6%)	10 (14.5%)
Long-acting	10 (28.6%)	2 (5.9%)	6 (17.1%)	2 (5.9%)
Blood glucose decreased				

Premixed/Intermediate-acting	8 (9.8%)	2 (2.9%)	5(6.1%)	1 (1.4%)
Long-acting	0	1 (2.9%)	0	1 (2.9%)

Data set: Safety analysis set during double blind period and safety analysis set during the long-term period

TEAE, Treatment-emergent adverse event

*Treatment duration: 52 weeks for saxagliptin→saxagliptin group (Week 0–52) and 36 weeks for placebo→saxagliptin group (Weeks 16–52).

Supplemental Table 9. Overall changes in body weight and vital signs throughout the study.

Variable		Saxagliptin→saxagliptin N = 117	Placebo→saxagliptin N = 115
Body weight (kg)			
Baseline	n	117	115
	Mean (SD)	64.28 (10.87)	66.61 (15.27)
Week 16	n	105	106
	Mean (SD)	65.09 (11.15)	66.31 (15.17)
Week 52	n	96	89
	Mean (SD)	65.02 (10.99)	67.08 (16.32)
Systolic blood pressure (mmHg)			
Baseline	n	117	115
	Mean (SD)	132.8 (16.5)	133.3 (13.7)
Week 16	n	105	106
	Mean (SD)	132.6 (15.1)	135.0 (14.2)
Week 52	n	96	89
	Mean (SD)	131.8 (13.5)	132.6 (14.6)
Diastolic blood pressure (mmHg)			
Baseline	n	117	115
	Mean (SD)	74.6 (10.6)	74.9 (10.8)
Week 16	n	105	106
	Mean (SD)	74.7 (9.8)	75.4 (11.0)
Week 52	n	96	89
	Mean (SD)	75.2 (9.2)	74.6 (10.4)
Pulse rate (beats/min)			

Baseline	n	117	115
	Mean (SD)	74.2 (12.2)	78.0 (11.4)
Week 16	n	105	106
	Mean (SD)	73.1 (11.5)	75.8 (10.3)
Week 52	n	96	89
	Mean (SD)	73.8 (11.5)	75.0 (10.8)
Temperature (°C)			
Baseline	n	117	115
	Mean (SD)	36.15 (0.40)	36.14 (0.39)
Week 16	n	105	106
	Mean (SD)	36.14 (0.41)	36.13 (0.39)
Week 52	n	96	89
	Mean (SD)	36.08 (0.50)	36.15 (0.42)

Data set: Safety analysis set during the long-term period.

SD, standard deviation

Baseline was defined as Week 0 in both groups.