

Online-Only Supplementary Materials

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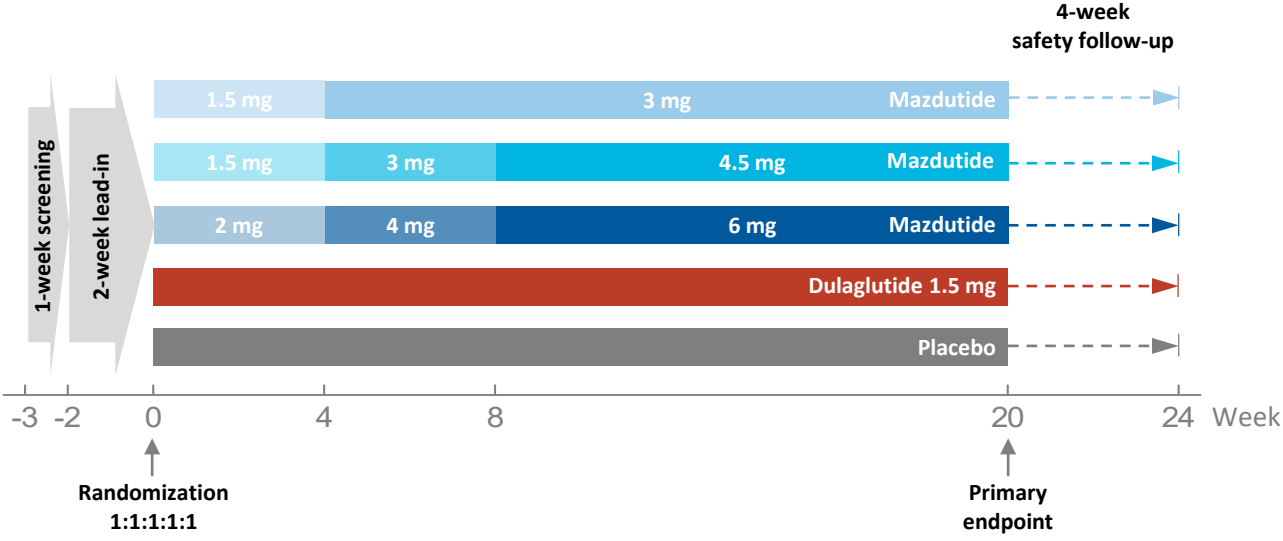
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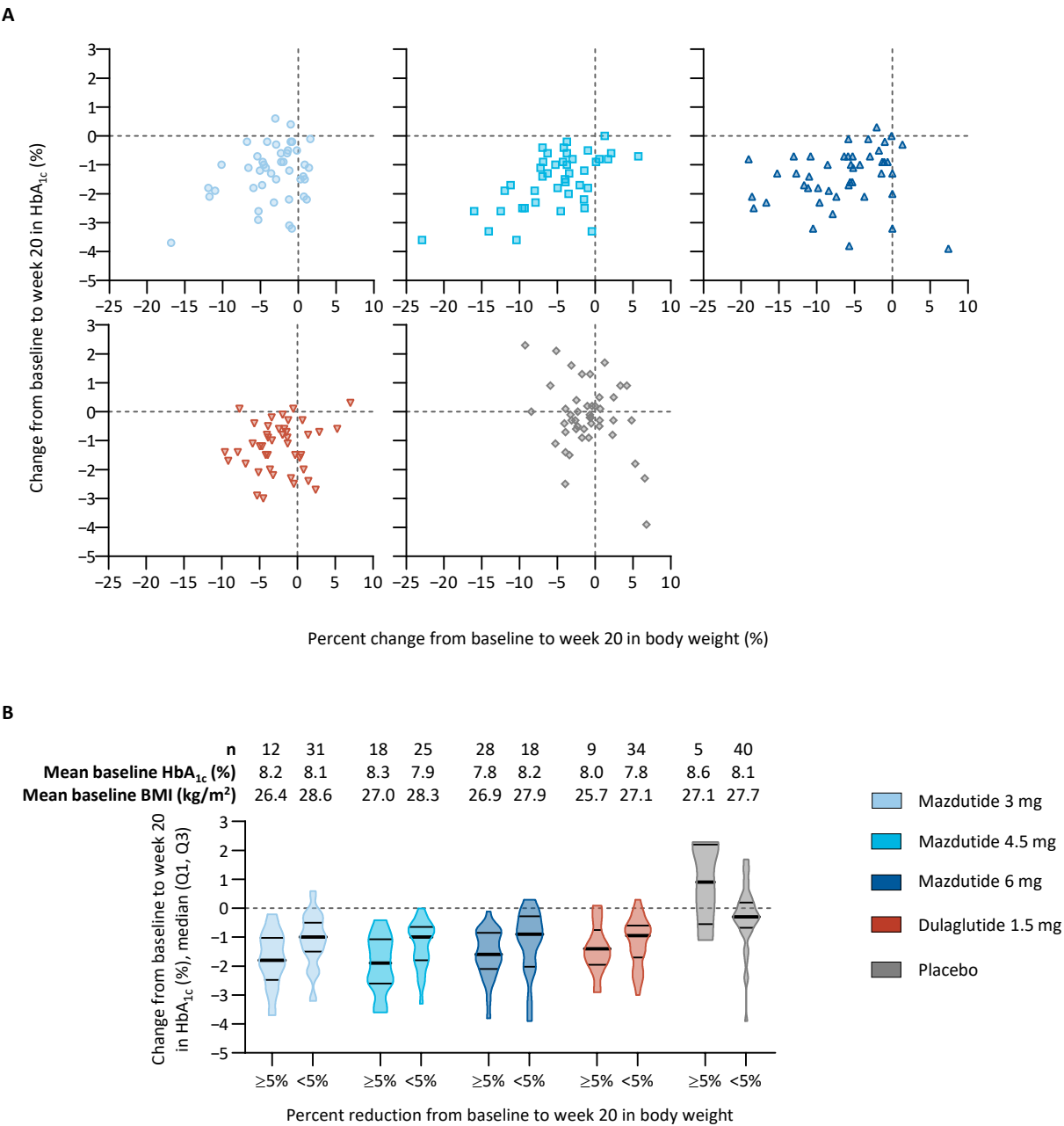
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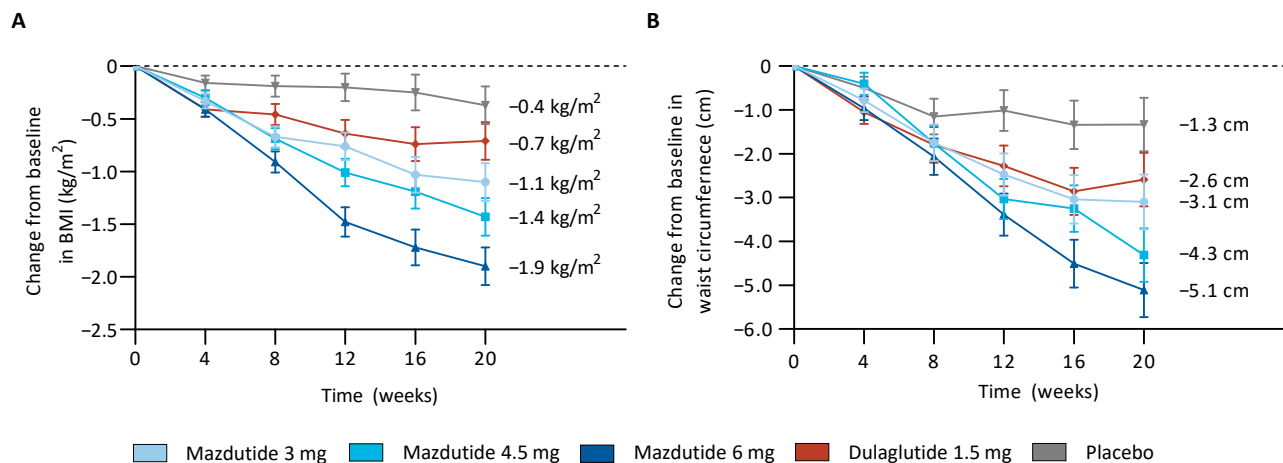


Supplementary Figure 1: Study design



Supplementary Figure 2: Changes in HbA_{1c} and body weight

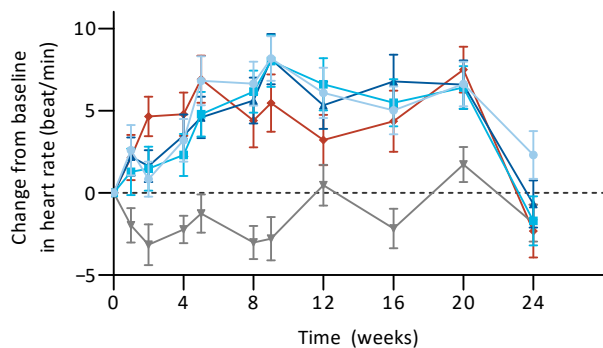
A. Change from baseline to week 20 in bodyweight and HbA_{1c} for each participant. **B.** Change from baseline to week 20 in HbA_{1c}, stratified by body weight loss category (percent reduction from baseline to week 20 $\geq 5\%$ or $< 5\%$). Data are presented as violin plots, with thick lines indicating medians and thin lines indicating interquartile ranges. Includes participants with week 20 measurement. BMI=body-mass index. HbA_{1c}=glycated hemoglobin A_{1c}.



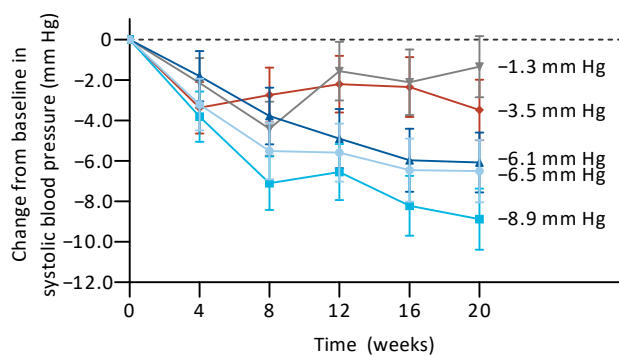
Supplementary Figure 3: Change from baseline in BMI (A) and waist circumference (B) over time

Data are least squares means \pm standard errors from MMRM analysis, mITT population. Mazdutide 3 mg $n = 50$; mazdutide 4.5 mg $n = 48$; mazdutide 6 mg $n = 49$; placebo $n = 51$; dulaglutide $n = 50$. BMI=body-mass index. MMRM=mixed model repeated measures.

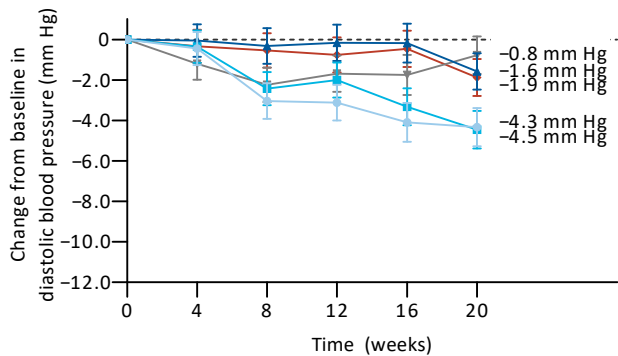
A



B



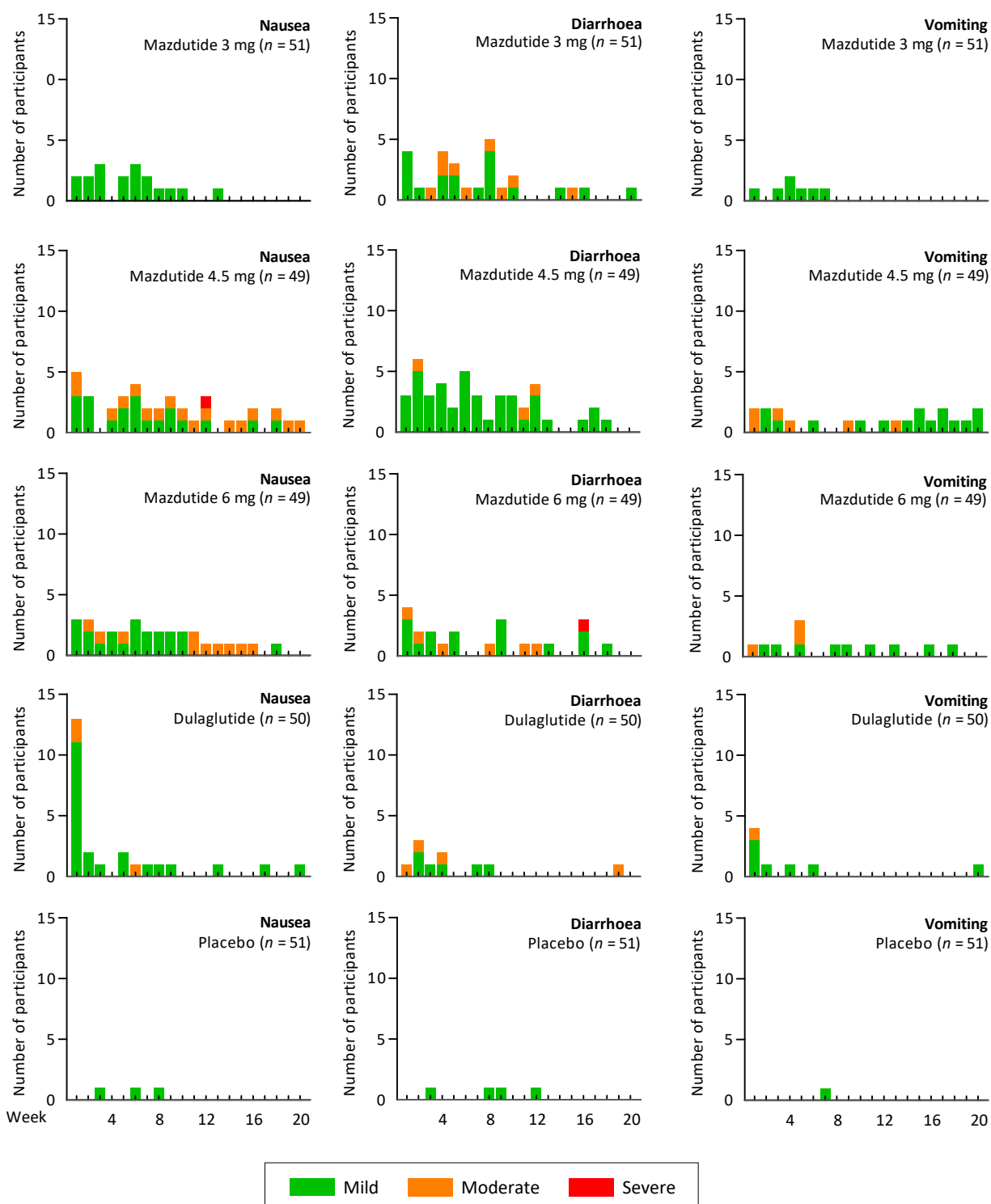
C



Legend: Mazdutide 3 mg (light blue), Mazdutide 4.5 mg (medium blue), Mazdutide 6 mg (dark blue), Dulaglutide 1.5 mg (red), Placebo (grey)

Supplementary Figure 4: Change from baseline in heart rate (A) and blood pressure (B and C) over time

Data are mean \pm SE for changes in heart rate, safety population; least squares means \pm SE for changes in blood pressure from MMRM analysis, mITT population. For safety population, mazdutide 3 mg $n = 51$; mazdutide 4.5 mg $n = 49$; mazdutide 6 mg $n = 49$; placebo $n = 51$; dulaglutide $n = 50$. For mITT population, mazdutide 3 mg $n = 50$; mazdutide 4.5 mg $n = 48$; mazdutide 6 mg $n = 49$; placebo $n = 51$; dulaglutide $n = 50$. MMRM=mixed model repeated measures. SE=standard error.



Supplementary Figure 5: By-week incidence of diarrhoea, nausea and vomiting over time

Safety population. For each study week, participants were counted once under each MedDRA preferred term and maximum severity.

Supplementary Table 1: Primary and secondary outcomes on glycemic parameters and body weight

	Mazdutide 3 mg (n = 50)		Mazdutide 4.5 mg (n = 48)		Mazdutide 6 mg (n = 49)		Dulaglutide 1.5 mg (n = 50)		Placebo (n = 51)
	Mean	p	Mean	p	Mean	p	Mean	p	Mean
Primary outcome									
Change from baseline to week 20 in HbA_{1c} (MMRM), %	-1.41 (0.15)		-1.67 (0.14)		-1.55 (0.14)		-1.35 (0.14)		0.03 (0.14)
Versus placebo	-1.44 (-1.84, -1.04)	<0.0001	-1.70 (-2.09, -1.30)	<0.0001	-1.58 (-1.98, -1.18)	<0.0001	-1.38 (-1.77, -0.98)	<0.0001	
Versus dulaglutide	-0.06 (-0.46, 0.34)	0.7513	-0.32 (-0.71, 0.08)	0.1120	-0.20 (-0.60, 0.20)	0.3213			
Change from baseline to week 20 in HbA_{1c} (ANCOVA), %	-1.31 (0.12)		-1.62 (0.13)		-1.45 (0.13)		-1.38 (0.12)		-0.14 (0.12)
Versus placebo	-1.17 (-1.51, -0.83)	<0.0001	-1.48 (-1.83, -1.14)	<0.0001	-1.31 (-1.66, -0.97)	<0.0001	-1.24 (-1.58, -0.89)	<0.0001	
Versus dulaglutide	0.07 (-0.28, 0.41)	0.6983	-0.24 (-0.59, 0.10)	0.1681	-0.08 (-0.42, 0.27)	0.6642			
Secondary outcomes									
Participants with HbA_{1c} <7.0% at week 20, n (%)	27 (54.0)		32 (66.7)		36 (73.5)		30 (60.0)		9 (17.6)
Odds ratio versus placebo	10.34 (3.93, 27.22)	<0.0001	17.91 (6.15, 52.21)	<0.0001	22.16 (7.49, 65.52)	<0.0001	13.00 (4.58, 36.86)	<0.0001	
Odds ratio versus dulaglutide	0.98 (0.40, 2.43)	0.9659	1.41 (0.53, 3.73)	0.4880	2.06 (0.74, 5.77)	0.1682			
Participants with HbA_{1c} ≤6.5% at week 20, n (%)	14 (28.0)		27 (56.3)		25 (51.0)		23 (46.0)		4 (7.8)
Odds ratio versus placebo	7.82 (2.39, 25.63)	0.0007	24.06 (6.92, 83.62)	<0.0001	18.72 (5.60, 62.58)	<0.0001	15.13 (4.43, 51.64)	<0.0001	
Odds ratio versus dulaglutide	0.60 (0.26, 1.37)	0.2243	1.66 (0.70, 3.99)	0.2526	1.34 (0.57, 3.16)	0.4994			
Participants with HbA_{1c} <5.7% at week 20, n (%)	4 (8.0)		5 (10.4)		3 (6.1)		5 (10.0)		1 (2.0)
Odds ratio versus placebo	7.85 (0.81, 76.46)	0.0761	8.92 (0.90, 88.24)	0.0613	6.65 (0.64, 68.83)	0.1120	7.24 (0.76, 69.38)	0.0858	
Odds ratio versus dulaglutide	1.09 (0.28, 4.17)	0.9048	1.16 (0.30, 4.44)	0.8248	0.89 (0.21, 3.76)	0.8777			
Change from baseline to week 20 in fasting plasma glucose, mmol/L	-1.40 (0.29)		-2.40 (0.28)		-2.58 (0.28)		-2.06 (0.28)		0.05 (0.28)
Versus placebo	-1.46 (-2.24, -0.67)	0.0003	-2.46 (-3.24, -1.68)	<0.0001	-2.63 (-3.41, -1.85)	<0.0001	-2.12 (-2.89, -1.34)	<0.0001	
Versus dulaglutide	0.66 (-0.13, 1.45)	0.1014	-0.34 (-1.12, 0.44)	0.3881	-0.52 (-1.30, 0.27)	0.1946			
Change from baseline to week 20 in 2-h postprandial glucose, mmol/L	-3.99 (0.50)		-5.55 (0.48)		-5.43 (0.48)		-4.78 (0.48)		-0.09 (0.48)
Versus placebo	-3.90 (-5.26, -2.54)	<0.0001	-5.46 (-6.80, -4.13)	<0.0001	-5.34 (-6.67, -4.02)	<0.0001	-4.69 (-6.01, -3.36)	<0.0001	
Versus dulaglutide	0.79 (-0.57, 2.14)	0.2529	-0.78 (-2.10, 0.55)	0.2479	-0.66 (-1.98, 0.66)	0.3260			
Change from baseline to week 20 in fasting insulin, mU/L	0.45 (0.93)		-1.55 (0.91)		-3.04 (0.90)		-0.19 (0.91)		-0.32 (0.90)
Versus placebo	0.77 (-1.76, 3.30)	0.5479	-1.23 (-3.73, 1.26)	0.3313	-2.72 (-5.21, -0.22)	0.0329	0.13 (-2.37, 2.64)	0.9181	
Versus dulaglutide	0.64 (-1.90, 3.18)	0.6193	-1.36 (-3.87, 1.14)	0.2851	-2.85 (-5.35, -0.35)	0.0258			
Percent change from baseline to week 20 in body weight, %	-4.12 (0.68)		-5.31 (0.67)		-7.11 (0.68)		-2.69 (0.67)		-1.38 (0.67)

	Mazdutide 3 mg (n = 50)		Mazdutide 4.5 mg (n = 48)		Mazdutide 6 mg (n = 49)		Dulaglutide 1.5 mg (n = 50)		Placebo (n = 51)
	Mean	p	Mean	p	Mean	p	Mean	p	Mean
Versus placebo	-2.74 (-4.62, -0.86)	0.0045	-3.92 (-5.78, -2.06)	<0.0001	-5.73 (-7.61, -3.85)	<0.0001	-1.31 (-3.18, 0.55)	0.1672	
Versus dulaglutide	-1.43 (-3.32, 0.46)	0.1367	-2.61 (-4.48, -0.75)	0.0062	-4.42 (-6.30, -2.53)	<0.0001			
Change from baseline to week 20 in body weight, kg	-3.02 (0.50)		-3.81 (0.48)		-5.29 (0.50)		-1.82 (0.49)		-0.97 (0.49)
Versus placebo	-2.05 (-3.42, -0.69)	0.0034	-2.85 (-4.20, -1.50)	<0.0001	-4.33 (-5.69, -2.96)	<0.0001	-0.86 (-2.21, 0.50)	0.2127	
Versus dulaglutide	-1.20 (-2.56, 0.17)	0.0867	-1.99 (-3.34, -0.64)	0.0041	-3.47 (-4.84, -2.10)	<0.0001			
Participants with ≥5% weight loss at week 20, n (%)	12 (24.0)		18 (37.5)		28 (57.1)		9 (18.0)		5 (9.8)
Odds ratio versus placebo	3.76 (1.27, 11.18)	0.0170	5.63 (1.85, 17.11)	0.0023	16.4 (5.23, 51.44)	<0.0001	2.34 (0.73, 7.49)	0.1507	
Odds ratio versus dulaglutide	1.61 (0.65, 4.03)	0.3065	2.41 (0.94, 6.15)	0.0657	7.10 (2.71, 18.58)	<0.0001			
Participants with ≥10% weight loss at week 20, n (%)	5 (10.0)		7 (14.6)		12 (24.5)		0		0
Odds ratio versus placebo	9.21 (1.07, 79.37)	0.0434	11.28 (1.35, 94.40)	0.0254	21.88 (2.70, 177.00)	0.0038			
Odds ratio versus dulaglutide	8.02 (0.95, 67.81)	0.0588	9.75 (1.18, 80.81)	0.0348	19.10 (2.42, 150.83)	0.0052			
Participants with ≥5% weight loss and HbA_{1c} <7.0% at week 20, n (%)	8 (16.0)		14 (29.2)		24 (49.0)		6 (12.0)		0
Odds ratio versus placebo	16.57 (2.04, 134.89)	0.0087	21.79 (2.66, 178.37)	0.0041	65.25 (8.18, 520.74)	<0.0001	9.68 (1.13, 82.56)	0.0380	
Odds ratio versus dulaglutide	1.68 (0.57, 4.94)	0.3479	2.79 (0.99, 7.85)	0.0517	7.87 (2.82, 21.99)	<0.0001			

Data are LSM (SE) for changes and percent changes from baseline and LSM (95% CI) for estimated treatment differences, from MMRM or ANCOVA analysis; n (%) and odds ratio (95% CI) for weight loss and HbA_{1c} target attainment rates, from Mantel-Haenszel analysis; mITT population. Proportion of participants reaching HbA_{1c} or weight loss targets was obtained by dividing the number of participants reaching respective targets at week 20 by the number of participants in the mITT population. ANCOVA=analysis of covariance. HbA_{1c}=glycated haemoglobin A1c. LSM=least squares mean. MMRM=mixed model repeated measures.

Supplementary Table 2: Exploratory outcomes on HOMA2-B and HOMA2-IR

	Mazdutide 3 mg (n = 50)		Mazdutide 4.5 mg (n = 48)		Mazdutide 6 mg (n = 49)		Dulaglutide 1.5 mg (n = 50)		Placebo (n = 51)
	Mean	p	Mean	p	Mean	p	Mean	p	Mean
HOMA2-B, % (derived from fasting insulin)									
Baseline	44.12 (28.869)		37.55 (21.463)		54.89 (78.594)		44.38 (29.278)		37.76 (17.517)
Change from baseline to week 20	15.40 (4.68)		26.85 (4.57)		20.79 (4.54)		27.48 (4.60)		2.55 (4.56)
Versus placebo	12.85 (0.06, 25.63)	0.0489	24.3 (11.68, 36.92)	0.0002	18.24 (5.63, 30.85)	0.0048	24.93 (12.25, 37.61)	0.0001	
HOMA2-IR (derived from fasting insulin)									
Baseline	1.736 (1.2873)		1.552 (1.0892)		2.430 (3.5252)		1.626 (1.9342)		1.510 (0.9235)
Change from baseline to week 20	-0.00 (0.13)		-0.31 (0.13)		-0.51 (0.13)		-0.11 (0.13)		0.00 (0.13)
Versus placebo	-0.00 (-0.36, 0.35)	0.9817	-0.31 (-0.66, 0.04)	0.0845	-0.52 (-0.87, -0.17)	0.0040	-0.11 (-0.46, 0.24)	0.5397	

Data are mean (SD) for baseline; LSM (SE) for changes from baseline and LSM (95% CI) for estimated treatment differences, from MMRM analysis, mITT population. LSM=least squares mean. MMRM=mixed model repeated measures. SD=standard deviation. SE=standard error.

Supplementary Table 3: Secondary outcomes on BMI, waist circumference and blood pressure

	Mazdutide 3 mg (n = 50)		Mazdutide 4.5 mg (n = 48)		Mazdutide 6 mg (n = 49)		Dulaglutide 1.5 mg (n = 50)		Placebo (n = 51)
	Mean	p	Mean	p	Mean	p	Mean	p	Mean
BMI, kg/m²									
Baseline	28.0 (4.8)		27.3 (3.8)		27.2 (3.4)		26.7 (3.2)		27.5 (3.5)
Change from baseline to week 20	-1.10 (0.18)		-1.43 (0.18)		-1.90 (0.18)		-0.71 (0.18)		-0.37 (0.18)
Versus placebo	-0.73 (-1.23, -0.23)	0.0046	-1.06 (-1.56, -0.56)	<0.0001	-1.53 (-2.03, -1.02)	<0.0001	-0.33 (-0.83, 0.16)	0.1863	
Versus dulaglutide	-0.39 (-0.90, 0.11)	0.1245	-0.72 (-1.22, -0.23)	0.0045	-1.19 (-1.69, -0.69)	<0.0001			
Waist circumference, cm									
Baseline	96.8 (11.0)		95.5 (9.3)		94.7 (9.2)		93.5 (8.8)		95.0 (9.0)
Change from baseline to week 20	-3.10 (0.63)		-4.31 (0.61)		-5.11 (0.62)		-2.59 (0.61)		-1.33 (0.61)
Versus placebo	-1.77 (-3.49, -0.05)	0.0441	-2.98 (-4.68, -1.29)	0.0006	-3.79 (-5.51, -2.06)	<0.0001	-1.26 (-2.97, 0.44)	0.1459	
Versus dulaglutide	-0.51 (-2.23, 1.22)	0.5629	-1.72 (-3.42, -0.02)	0.0470	-2.52 (-4.24, -0.80)	0.0043			
Systolic blood pressure, mm Hg									
Baseline	128.5 (13.1)		130.5 (11.2)		128.9 (11.7)		125.6 (13.3)		128.7 (12.8)
Change from baseline to week 20	-6.50 (1.55)		-8.87 (1.52)		-6.08 (1.48)		-3.47 (1.50)		-1.34 (1.52)
Versus placebo	-5.17 (-9.42, -0.91)	0.0173	-7.53 (-11.73, -3.33)	0.0004	-4.74 (-8.89, -0.59)	0.0252	-2.14 (-6.31, 2.04)	0.3158	
Versus dulaglutide	-3.03 (-7.26, 1.20)	0.1597	-5.40 (-9.57, -1.22)	0.0113	-2.60 (-6.73, 1.52)	0.2156			
Diastolic blood pressure, mm Hg									
Baseline	82.3 (8.6)		82.6 (7.9)		82.6 (8.1)		80.9 (8.6)		82.0 (6.8)
Change from baseline to week 20	-4.32 (0.95)		-4.46 (0.93)		-1.58 (0.91)		-1.87 (0.92)		-0.77 (0.93)
Versus placebo	-3.55 (-6.17, -0.94)	0.0077	-3.69 (-6.27, -1.11)	0.0050	-0.81 (-3.36, 1.74)	0.5342	-1.10 (-3.66, 1.47)	0.4013	
Versus dulaglutide	-2.46 (-5.05, 0.14)	0.0637	-2.60 (-5.16, -0.03)	0.0472	0.29 (-2.24, 2.82)	0.8229			

Data are LSM (SE) for changes and percent changes from baseline and LSM (95% CI) for estimated treatment differences, from MMRM analysis, mITT population. BMI=body-mass index. LSM=least squares mean. MMRM=mixed model repeated measures. SE=standard error.

Supplementary Table 4: Secondary outcomes on lipids panel, transaminase and serum uric acid

	Mazdutide 3 mg (n = 50)		Mazdutide 4.5 mg (n = 48)		Mazdutide 6 mg (n = 49)		Dulaglutide 1.5 mg (n = 50)		Placebo (n = 51)
	Mean	p	Mean	p	Mean	p	Mean	p	Mean
Total cholesterol									
Baseline, mmol/L	4.8 (4.2–5.5)		4.5 (4.0–5.1)		4.4 (3.8–5.0)		4.3 (4.0–5.0)		4.5 (4.1–5.0)
Change from baseline to week 20, mmol/L	–0.09 (0.13)		–0.23 (0.13)		–0.44 (0.12)		0.17 (0.12)		0.46 (0.13)
Percent change from baseline to week 20, %	–0.03 (3.12)		–2.54 (3.01)		–9.53 (2.97)		4.67 (2.99)		11.93 (3.01)
Versus placebo	–11.96 (–20.43, –3.49)	0.0059	–14.47 (–22.79, –6.15)	0.0007	–21.46 (–29.69, –13.23)	<0.0001	–7.26 (–15.53, 1.02)	0.0852	
Versus dulaglutide	–4.70 (–13.17, 3.77)	0.2754	–7.21 (–15.50, 1.08)	0.0878	–14.20 (–22.36, –6.03)	0.0007			
LDL cholesterol									
Baseline, mmol/L	3.1 (2.7–3.6)		2.9 (2.7–3.4)		2.8 (2.4–3.3)		2.9 (2.5–3.3)		2.9 (2.5–3.4)
Change from baseline to week 20, mmol/L	–0.05 (0.10)		–0.17 (0.10)		–0.32 (0.09)		0.11 (0.09)		0.24 (0.10)
Percent change from baseline to week 20, %	1.25 (3.85)		–2.79 (3.72)		–10.61 (3.66)		5.05 (3.68)		11.84 (3.71)
Versus placebo	–10.59 (–21.04, –0.14)	0.0471	–14.63 (–24.90, –4.36)	0.0055	–22.45 (–32.59, –12.30)	<0.0001	–6.79 (–16.98, 3.41)	0.1906	
Versus dulaglutide	–3.80 (–14.22, 6.63)	0.4732	–7.84 (–18.07, 2.38)	0.1319	–15.66 (–25.73, –5.59)	0.0025			
HDL cholesterol									
Baseline, mmol/L	1.2 (1.0–1.4)		1.1 (0.9–1.3)		1.1 (1.0–1.3)		1.1 (0.9–1.3)		1.2 (1.0–1.3)
Change from baseline to week 20, mmol/L	–0.06 (0.03)		0.01 (0.03)		–0.02 (0.02)		0.05 (0.02)		0.07 (0.03)
Percent change from baseline to week 20, %	–3.47 (2.36)		1.61 (2.30)		–0.47 (2.26)		5.92 (2.27)		6.96 (2.29)
Versus placebo	–10.43 (–16.85, –4.01)	0.0016	–5.35 (–11.70, 1.00)	0.0983	–7.44 (–13.70, –1.17)	0.0202	–1.04 (–7.34, 5.25)	0.7446	
Versus dulaglutide	–9.39 (–15.77, –3.01)	0.0042	–4.31 (–10.62, 2.00)	0.1798	–6.40 (–12.62, –0.17)	0.0440			
Triglycerides									
Baseline, mmol/L	1.7 (1.3–2.5)		1.6 (1.2–2.3)		2.1 (1.2–3.0)		1.6 (1.1–2.3)		1.8 (1.2–2.5)
Change from baseline to week 20, mmol/L	–0.23 (0.15)		–0.52 (0.15)		–0.77 (0.14)		–0.26 (0.14)		0.34 (0.15)
Percent change from baseline to week 20, %	–1.46 (6.60)		–16.98 (6.43)		–29.97 (6.32)		–3.73 (6.37)		23.94 (6.43)
Versus placebo	–25.40 (–43.38, –7.42)	0.0059	–40.93 (–58.70, –23.16)	<0.0001	–53.91 (–71.45, –36.37)	<0.0001	–27.67 (–45.38, –9.97)	0.0023	
Versus dulaglutide	2.27 (–15.63, 20.18)	0.8025	–13.25 (–30.90, 4.39)	0.1401	–26.24 (–43.71, –8.77)	0.0034			
Alanine aminotransferase									
Baseline, U/L	18.0 (13.0–27.0)		21.0 (13.0–34.0)		18.0 (14.0–24.0)		18.0 (14.0–30.0)		23.0 (15.0–33.0)

	Mazdutide 3 mg (n = 50)		Mazdutide 4.5 mg (n = 48)		Mazdutide 6 mg (n = 49)		Dulaglutide 1.5 mg (n = 50)		Placebo (n = 51)
	Mean	p	Mean	p	Mean	p	Mean	p	Mean
Change from baseline to week 20, U/L	-4.89 (1.77)		-7.28 (1.74)		-7.09 (1.71)		-3.63 (1.71)		-2.24 (1.73)
Percent change from baseline to week 20, %	-12.62 (8.64)		-15.83 (8.46)		-21.23 (8.30)		6.05 (8.32)		-3.57 (8.43)
Versus placebo	-9.05 (-32.61, 14.51)	0.4497	-12.25 (-35.50, 11.00)	0.3000	-17.66 (-40.76, 5.44)	0.1332	9.62 (-13.50, 32.74)	0.4130	
Versus dulaglutide	-18.67 (-42.08, 4.74)	0.1174	-21.87 (-45.04, 1.30)	0.0641	-27.28 (-50.14, -4.41)	0.0196			
Aspartate aminotransferase									
Baseline, U/L	19.0 (16.0–29.0)		20.0 (16.0–28.0)		19.0 (17.0–24.0)		20.5 (17.0–27.0)		21.0 (17.0–28.0)
Change from baseline to week 20, U/L	-4.22 (1.54)		-4.71 (1.50)		-4.48 (1.48)		-1.29 (1.48)		-1.25 (1.50)
Percent change from baseline to week 20, %	-10.13 (6.20)		-14.78 (6.05)		-12.70 (5.96)		6.45 (5.99)		-3.63 (6.05)
Versus placebo	-6.51 (-23.43, 10.42)	0.4492	-11.15 (-27.83, 5.54)	0.1891	-9.08 (-25.67, 7.51)	0.2820	10.08 (-6.50, 26.66)	0.2320	
Versus dulaglutide	-16.59 (-33.41, 0.23)	0.0532	-21.23 (-37.81, -4.65)	0.0124	-19.15 (-35.64, -2.67)	0.0230			
Serum uric acid									
Baseline, µmol/L	327.86 (91.747)		310.51 (74.545)		315.01 (75.175)		313.63 (94.457)		303.44 (99.964)
Change from baseline to week 20, µmol/L	-1.97 (9.69)		-7.00 (9.42)		-15.38 (9.25)		7.39 (9.34)		-0.49 (9.42)
Percent change from baseline to week 20, %	0.93 (3.16)		-1.52 (3.07)		-4.50 (3.02)		3.99 (3.05)		1.91 (3.07)
Versus placebo	-0.98 (-9.60, 7.63)	0.8222	-3.43 (-11.92, 5.06)	0.4267	-6.41 (-14.80, 1.98)	0.1337	2.08 (-6.37, 10.53)	0.6276	
Versus dulaglutide	-3.06 (-11.61, 5.48)	0.4804	-5.51 (-13.96, 2.94)	0.2000	-8.49 (-16.85, -0.13)	0.0465			

Data are mean (SD) or median (interquartile range) for baseline; LSM (SE) for changes and percent changes from baseline and LSM (95% CI) for estimated treatment differences, from MMRM analysis, mITT population. CFB=change from baseline. HDL=high-density lipoprotein. LDL=low-density lipoprotein. LSM=least squares mean. MMRM=mixed model repeated measures. SD=standard deviation. SE=standard error.

Supplementary Table 5: Hypoglycemic episodes

	Mazdutide 3 mg (n =51)	Mazdutide 4.5 mg (n = 49)	Mazdutide 6 mg (n = 49)	Dulaglutide 1.5 mg (n = 50)	Placebo (n = 51)
Any hypoglycaemia	3 (5.9) [4]	4 (8.2) [6]	8 (16.3) [13]	1 (2.0) [2]	4 (7.8) [5]
Severe	0	0	0	0	0
Documented symptomatic	1 (2.0) [1]	0	0	0	0
Asymptomatic	1 (2.0) [1]	3 (6.1) [5]	6 (12.2) [7]	1 (2.0) [2]	3 (5.9) [4]
Probable symptomatic	1 (2.0) [2]	1 (2.0) [1]	3 (6.1) [5]	0	1 (2.0) [1]
Pseudo-	0	0	1 (2.0) [1]	0	0

Data are n (%) [number of events], safety population. American Diabetes Association 2013 classification of hypoglycemia.

Supplementary Table 6: Laboratory safety outcomes and immunogenicity

	Mazdutide 3 mg (n = 51)	Mazdutide 4.5 mg (n = 49)	Mazdutide 6 mg (n = 49)	Dulaglutide 1.5 mg (n = 50)	Placebo (n = 51)
Participants with ≥ 3 times upper limit of normal ALT, n (%)	0	0	0	0	0
Participants with ≥ 3 times upper limit of normal AST, n (%)	0	0	0	1 (2.0)	0
Participants with ≥ 3 times upper limit of normal lipase, n (%)	0	0	0	1 (2.0)	0
Participants with ≥ 3 times upper limit of normal amylase, n (%)	0	0	0	0	0
Calcitonin ≥ 20 ng/L, n (%)	0	0	0	0	0
Participants with mazdutide anti-drug antibodies (ADA), n (%)					
At baseline	0	3 (6.1)	3 (6.1)		
Post baseline treatment-induced ADA	5 (9.8)	10 (20.4)	9 (18.4)		
Post baseline treatment-emergent ADA	0	0	0		

Data are n (%), safety population. All percentages are relative to the total number of participants in each treatment group in the safety population. A subject is considered to be treatment-induced ADA positive if the participant is ADA negative at baseline and has at least one post baseline positive measurement. A participant is considered to be treatment-emergent ADA positive if the participant is ADA positive at baseline and has at least one post baseline titre that is a 4-fold or greater increase in titre from baseline measurement.