ONLINE-ONLY SUPPLEMENTAL MATERIAL

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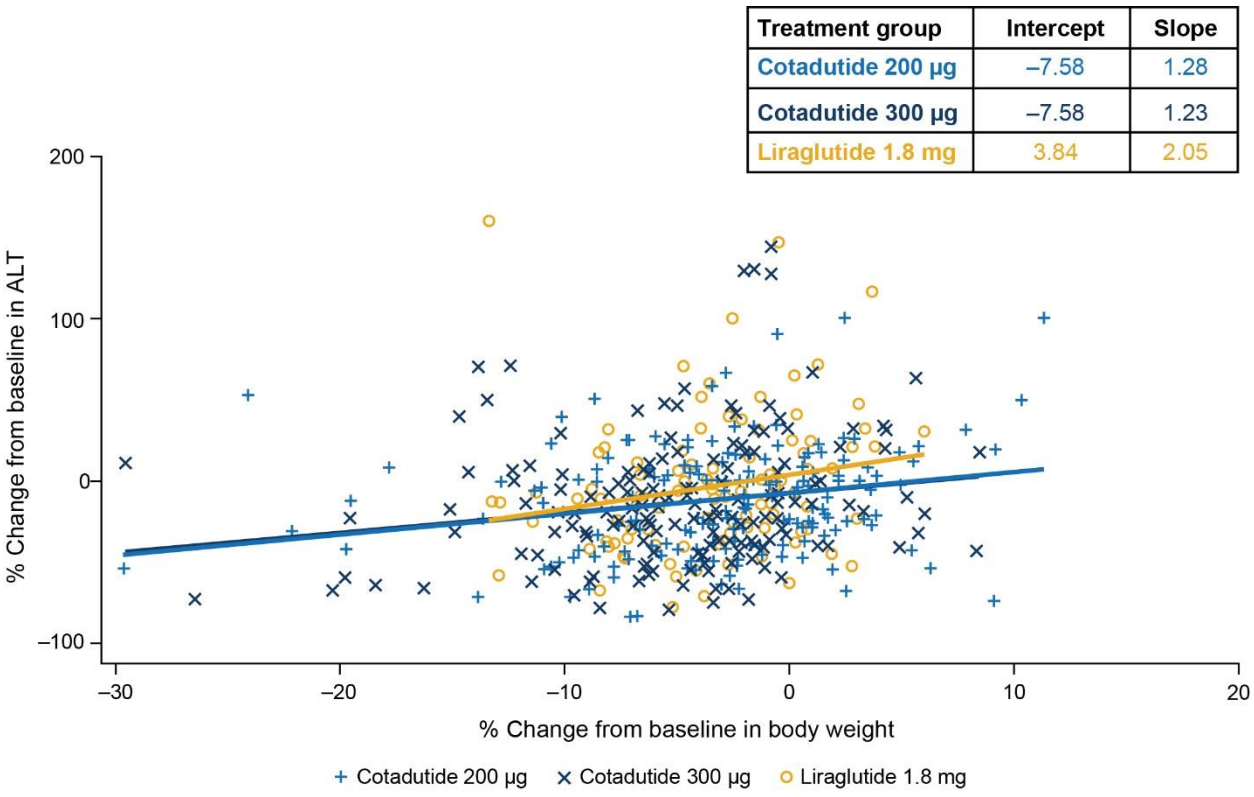
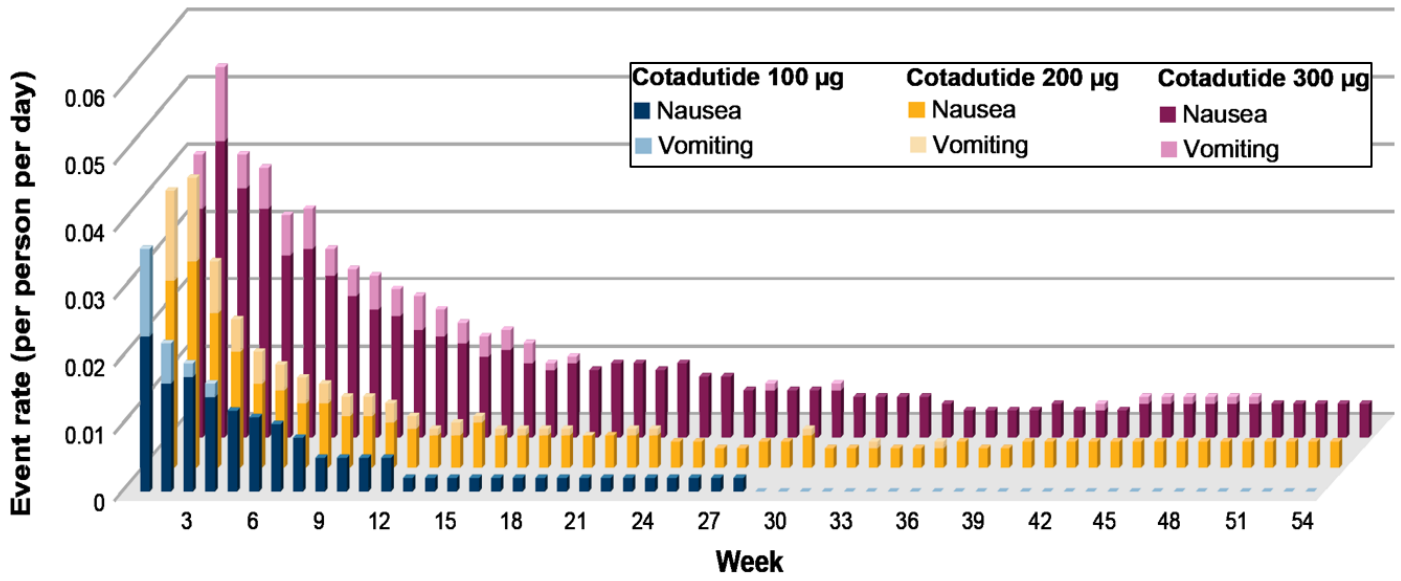
Supplementary Figure 1. Scatter plot of percent change from baseline in body weight versus percent change from baseline in ALT, with corresponding least squares regression lines. ALT, alanine aminotransferase.



Supplementary Figure 2. The event rate of gastrointestinal adverse events with cotadutide treatment from week 1 to week 54 (per-protocol population).



Supplementary Table 1. Patient demographics and baseline characteristics. Data are mean (SD), unless otherwise specified; ITT population, unless otherwise specified.

Parameter	Cotadutide 100 µg (n=100)	Cotadutide 200 µg (n=256)	Cotadutide 300 µg (n=256)	Liraglutide 1.8 mg (n=110)	Placebo (n=112)
Age, years	57.6 (9.9)	57.3 (9.9)	56.3 (10.2)	55.5 (9.8)	57.3 (9.5)
Sex, n (%)					
Male	43 (43)	109 (43)	127 (50)	50 (46)	57 (51)
Female	57 (57)	147 (57)	129 (50)	60 (55)	55 (49)
Race, n (%)					
Asian	0	3 (1)	1 (0.4)	1 (1)	1 (1)
Black	1 (1)	3 (1)	3 (1)	3 (3)	0
White	99 (99)	245 (96)	252 (98)	103 (94)	107 (96)
Other	0	5 (2)	0	3 (3)	4 (4)
Body weight, kg	99.0 (20.3)	98.1 (20.2)	100.8 (19.6)	102.1 (22.7)	98.1 (19.8)
BMI, kg/m^2	35.0 (5.7)	34.9 (5.4)	35.2 (5.4)	35.4 (6.1)	34.2 (5.1)
FPG, **mg/dL**	184.4 (45.5)	189.7 (49.8)	185.8 (50.5)	184.9 (55.8)	183.2 (47.5)
HbA1c, %	8.1 (0.9)	8.2 (1.0)	8.1 (1.1)	8.1 (1.0)	8.2 (1.1)
HbA1c, mmol/mol	65 (9.8)	66 (10.9)	65 (12.0)	65 (10.9)	66 (12.0)
≤8% (64 mmol/mol), n (%)	50 (50)	128 (50)	130 (51)	54 (49)	54 (48)
>8% (64 mmol/mol), n (%)	50 (50)	128 (50)	126 (49)	56 (51)	58 (52)
Type 2 diabetes duration, years	7.5 (5.3)	7.7 (5.6)	7.6 (6.0)	7.6 (6.1)	7.6 (5.0)
HMG-CoA reductase inhibitors[*] [†]	39 (39.0)	99 (38.7)	123 (48.0)	46 (41.8)	46 (41.1)

Cardiovascular parameters					
Systolic BP, mmHg	134.6 (12.3)	132.8 (12.2)	133.7 (12.0)	136.5 (11.4)	132.1 (14.1)
Diastolic BP, mmHg	81.0 (7.7)	81.1 (7.6)	81.8 (7.7)	81.8 (8.1)	80.3 (8.3)
Pulse rate, bpm	73.6 (8.6)	74.6 (9.8)	74.9 (9.9)	76.4 (11.0)	73.2 (10.1)
Lipid parameters					
Total cholesterol, mg/dL	186.2 (34.6)	187.1 (45.6)	189.3 (50.9)	196.0 (50.7)	191.9 (46.9)
Triglycerides, mg/dL	216.8 (141.3)	215.5 (125.2)	227.9 (181.5)	239.7 (150.0)	215.9 (140.7)
HDL, mg/dL	45.3 (10.9)	44.9 (11.9)	45.4 (12.0)	46.9 (13.6)	44.7 (10.4)
LDL, mg/dL	102.3 (27.6)	100.6 (38.7)	101.2 (40.8)	101.7 (38.6)	106.1 (39.5)
Hepatic parameters*					
AST, U/L	24.8 (12.3)	24.1 (13.3)	25.1 (17.4)	24.6 (11.9)	23.7 (11.5)
ALT, U/L	33.5 (21.6)	32.1 (18.1)	33.2 (18.7)	32.8 (18.2)	30.7 (19.2)
GGT, U/L	40.3 (40.9)	42.5 (32.1)	45.1 (48.8)	48.1 (49.5)	41.5 (30.1)
FIB-4	1.1 (0.7)	1.1 (0.6)	1.1 (0.8)	1.1 (0.6)	1.1 (0.5)
NFS	–0.54 (1.31)	–0.58 (1.15)	–0.63 (1.29)	–0.50 (1.09)	–0.51 (1.01)
FLI	85.6 (16.1)	86.8 (16.4)	87.5 (17.3)	87.4 (16.8)	85.0 (16.1)

*Per-protocol population: cotadutide 100 µg, n = 76; cotadutide 200 µg, n = 202; cotadutide 300 µg, n = 189; liraglutide 1.8 mg, n = 104; placebo, n = 93.

†Started prior to first randomized dose and continued afterwards.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; FIB-4, fibrosis-4 index; FLI, fatty liver index; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HMG-CoA, β-Hydroxy β-methylglutaryl-CoA; ITT, intent-to-treat; NFS, nonalcoholic fatty liver disease fibrosis score.

Supplementary Table 2. Percent change in secondary and exploratory efficacy endpoints from baseline to week 54. Data are intent-to-treat population, unless otherwise specified.

Parameter	Cotadutide 100 µg (n=100)	Cotadutide 200 µg (n=256)	Cotadutide 300 µg (n=256)	Liraglutide 1.8 mg (n=110)	Placebo (n=112)
Body weight, kg, LS mean (95% CI)	−3.20 (−4.28, −2.12)	−3.09 (−3.77, −2.42)	−4.35 (−5.03, −3.68)	−2.94 (−3.96, −1.92)	−0.94 (−1.94, 0.07)
P vs placebo	0.003	< 0.001	< 0.001	0.006	—
P vs liraglutide	0.730	0.804	0.023	—	—
Waist circumference, cm, LS mean (95% CI)	−3.73 (−5.54, −1.91)	−4.29 (−5.42, −3.16)	−4.86 (−6.00, −3.72)	−4.15 (−5.86, −2.43)	−1.77 (−3.47, −0.07)
P vs placebo	0.123	0.015	0.003	0.054	—
FPG, mg/dL, LS mean (95% CI)	−30.65 (−38.52, −22.77)	−39.86 (−44.77, −34.95)	−40.10 (−45.03, −35.16)	−39.50 (−46.98, −32.03)	−14.41 (−21.82, −7.00)
P vs placebo	0.003	< 0.001	< 0.001	< 0.001	
HOMA IR, LS mean (95% CI)	−0.12 (−0.35, 0.12)	0.10 (−0.05, 0.25)	−0.07 (−0.22, 0.08)	0.04 (−0.18, 0.26)	0.04 (−0.18, 0.26)
P vs placebo	0.334	0.659	0.420	0.998	—

FPG, fasting plasma glucose; HOMA IR, homeostatic model assessment of insulin resistance; LS, least squares.

Supplementary Table 3. Effect of cotadutide on aspartate aminotransferase levels by quartile at week 54 (per-protocol population).

Parameter	Cotadutide 100 µg	Cotadutide 200 µg	Cotadutide 300 µg	Liraglutide 1.8 mg	Placebo
First quartile, n*	18	49	47	26	23
Baseline†	14.2 (1.8)	13.4 (1.6)	13.5 (1.5)	13.7 (1.6)	14.0 (1.7)
Week 54‡	7.3 (−7.5, 22.2)	12.1 (3.1, 21.0)	11.8 (2.7, 20.9)	26.1 (14.0, 38.3)	16.3 (3.3, 29.3)
P vs placebo§	0.372	0.600	0.579	0.275	—
P vs liraglutide§	0.055	0.068	0.064	—	—
Second quartile, n*	20	46	47	26	20
Baseline†	18.7 (1.1)	17.6 (1.1)	17.6 (1.3)	19.2 (1.3)	18.1 (0.8)
Week 54‡	10.7 (−5.1, 26.5)	5.9 (−4.6, 16.3)	−5.9 (−16.4, 4.6)	-0.9 (-15.7, 13.9)	−6.3 (−21.9, 9.3)
P vs placebo§	0.132	0.202	0.966	0.621	—
P vs liraglutide§	0.273	0.475	0.604	—	—
Third quartile, n*	19	54	47	23	26
Baseline†	23.7 (2.4)	22.6 (1.7)	23.1 (2.2)	24.7 (1.9)	22.2 (1.7)
Week 54‡	−8.7 (−23.9, 6.6)	−10.5 (−19.5, −1.4)	−8.0 (−17.6, 1.7)	−0.4 (−14.8, 13.9)	10.8 (−3.0, 24.2)
P vs placebo§	0.061	0.010	0.026	0.270	—
P vs liraglutide§	0.431	0.254	0.392	—	—
Fourth quartile, n*	19	53	48	29	24
Baseline†	42.2 (12.2)	41.3 (15.0)	45.9 (23.8)	38.9 (12.8)	39.3 (12.2)
Week 54‡	−14.4 (−31.9, 3.2)	−29.2 (−39.7, −18.7)	−33.8 (−44.9, −22.7)	−24.6 (−38.8, −10.3)	4.1 (−11.7, 19.8)
P vs placebo§	0.124	<0.001	<0.001	0.008	—
P vs liraglutide§	0.376	0.606	0.317	—	—

*n values are for week 54 data; per-protocol population.

†Data are mean (u/L) (standard deviation).

‡Data are least squares mean % change from baseline (95% CI).

§ *P* values were unadjusted for multiplicity.

Supplementary Table 4. Effect of cotadutide on alanine aminotransferase levels by quartile, at week 54 (per-protocol population).

Parameter	Cotadutide 100 µg	Cotadutide 200 µg	Cotadutide 300 µg	Liraglutide 1.8 mg	Placebo
First quartile, n*	19	50	46	23	23
Baseline†	15.3 (2.1)	16.2 (3.0)	15.6 (2.8)	14.9 (3.2)	13.7 (3.2)
Week 54‡	9.2 (−8.5, 26.9)	6.7 (−4.3, 17.6)	9.1 (−2.1, 20.3)	28.9 (13.0, 44.8)	9.8 (−6.4, 26.1)
P vs placebo§	0.958	0.756	0.945	0.096	—
P vs liraglutide§	0.104	0.025	0.047	—	—
Second quartile, n*	19	39	48	27	18
Baseline†	23.4 (1.9)	22.8 (1.5)	22.5 (2.2)	23.5 (2.6)	22.0 (1.7)
Week 54‡	−6.9 (−27.9, 14.1)	1.1(−13.5, 15.8)	−5.5 (−18.7, 7.7)	−8.6 (−26.5, 9.3)	2.3 (−20.0, 24.6)
P vs placebo§	0.556	0.932	0.552	0.460	—
P vs liraglutide§	0.904	0.405	0.786	—	—
Third quartile, n*	19	60	47	26	26
Baseline†	31.6 (3.4)	30.2 (3.6)	34.1 (4.0)	33.5 (3.6)	28.4 (2.3)
Week 54‡	−12.6 (−28.5, 3.2)	−16.9 (−26.1, −7.6)	−19.8 (−30.5, −9.1)	−1.3 (−15.1, 12.5)	−4.8 (−19.1, 9.6)
P vs placebo§	0.468	0.148	0.118	0.741	—
P vs liraglutide§	0.289	0.072	0.032	—	—
Fourth quartile, n*	19	53	48	28	26
Baseline†	63.9 (22.2)	56.1 (18.6)	59.8 (14.9)	55.7 (18.2)	54.2 (20.7)
Week 54‡	−18.5 (−34.8, −2.3)	−33.3 (−42.9, −23.6)	−37.5 (−47.7, −27.3)	−29.2 (−42.5, −15.8)	−6.2 (−20.1, 7.6)
P vs placebo§	0.259	0.002	<0.001	0.020	—
P vs liraglutide§	0.321	0.623	0.328	—	—

*n values are for week 54 data; per-protocol population.

†Data are mean (u/L) (standard deviation).

‡Data are least squares mean % change from baseline (95% confidence interval).

§*P* values were unadjusted for multiplicity.

Supplementary Table 5. Summary of safety and TEAEs by SOC and PT that occurred in ≥15% of patients in any treatment arm. Data are as-treated population.

Parameter	Cotadutide 100 µg (n=100)	Cotadutide 200 µg (n=256)	Cotadutide 300 µg (n=256)	Liraglutide 1.8 mg (n=110)	Placebo (n=112)
TEAEs, n (%)	73 (73.0)	202 (78.9)	206 (80.5)	68 (61.8)	69 (61.6)
Treatment-related TEAEs	46 (46.0)	148 (57.8)	155 (60.5)	25 (22.7)	24 (21.4)
Leading to discontinuation	13 (13.0)	39 (15.2)	55 (21.5)	2 (1.8)	5 (4.5)
SAEs, n (%)	12 (12.0)	33 (12.9)	20 (7.8)	8 (7.3)	12 (10.7)
Treatment-related SAEs	1 (1.0)	1 (0.4)	0	0	1 (0.9)
Deaths, n (%)	0	2 (0.8)*	1 (0.4) †	0	0
AEs by SOC and PT, n (%)					
Gastrointestinal disorders	41 (41.0)	149 (58.2)	152 (59.4)	30 (27.3)	31 (27.7)
Diarrhea	13 (13.0)	49 (19.1)	28 (10.9)	4 (3.6)	10 (8.9)
Nausea	23 (23.0)	85 (33.2)	105 (41.0)	17 (15.5)	12 (10.7)
Vomiting	10 (10.0)	51 (19.9)	43 (16.8)	3 (2.7)	5 (4.5)
ADA positive post-baseline, n (%)	55 (56.7)	152 (61.3)	155 (62.0)	NA	3 (2.7)
n	97	248	250	NA	111
Median of maximum titer‡	20.0	20.0	20.0	NA	5.0
Range	5, 2560	5, 640	5, 5120	NA	5, 20

*Due to myocardial infarction (n=1) and hemorrhagic stroke (n=1).

†Due to pulmonary edema (n=1).

‡Includes all post-baseline, ADA-positive assessments with reportable ADA titer results.

ADA, antidrug antibody; Admin, administration; AE, adverse event; PT, preferred term; NA, not available; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.

Supplementary Table 6. Additional TEAEs by SOC and PT that occurred in ≥ 15% of patients in any treatment arm (as-treated population).

Parameter, n (%)	Cotadutide 100 µg (n=100)	Cotadutide 200 µg (n=256)	Cotadutide 300 µg (n=256)	Liraglutide 1.8 mg (n=110)	Placebo (n=112)
General disorders and administration-site conditions	16 (16.0)	44 (17.2)	50 (19.5)	4 (3.6)	8 (7.1)
Infections and infestations	33 (33.0)	99 (38.7)	90 (35.2)	35 (31.8)	38 (33.9)
Musculoskeletal and connective tissue disorders	18 (18.0)	40 (15.6)	36 (14.1)	11 (10.0)	13 (11.6)
Nervous system disorders	12 (12.0)	40 (15.6)	41 (16.0)	10 (9.1)	8 (7.1)

Supplementary Table 7. Change from baseline to week 54 in vital signs (as-treated population).

Parameter, LS mean (95% CI)	Cotadutide 100 µg (n=100)	Cotadutide 200 µg (n=256)	Cotadutide 300 µg (n=256)	Liraglutide 1.8 mg (n=110)	Placebo (n=112)
Systolic BP, mmHg	−3.99	−3.34	−4.46	−3.30	−1.46
	(−6.09, −1.89)	(−4.65, −2.04)	(−5.77, −3.14)	(−5.29, −1.30)	(−3.44, 0.51)
P vs placebo	0.085	0.119	0.013	–	–
Diastolic BP, mmHg	−1.31	−0.61	−0.76	−0.94	−0.86
	(−2.66, 0.04)	(−1.45, 0.24)	(−1.61, 0.09)	(−2.22, 0.35)	(−2.13, 0.41)
P vs placebo	0.633	0.746	0.899	–	–
Pulse rate, BPM	3.1	2.6	3.1	1.9	−0.1
	(1.4, 4.8)	(1.5, 3.6)	(2.0, 4.1)	(0.3, 3.5)	(−1.7, 1.5)
P vs placebo	0.006	0.005	0.001	–	–

BP, blood pressure; BPM, beats per minute; LS, least squares.