Appendix 1: Search strings

PubMed:

("glucagon-like peptide-1/glucagon dual agonist" [tiab] OR "twincretin" [tiab] OR "cotadutide" [tiab] OR "MEDI0382" [tiab]) AND ("type 2 diabetes" [tiab] OR "type 2 diabetes mellitus" [tiab] OR "non-insulin dependent diabetes mellitus" [tiab] OR "T2DM" [tiab] OR "T2D" [tiab])

Scopus:

(TITLE-ABS-KEY("glucagon-like peptide-1/glucagon dual agonist" OR "twincretin" OR "cotadutide" OR "MEDI0382")) AND TITLE-ABS-KEY("type 2 diabetes" OR "type 2 diabetes mellitus" OR "non-insulin dependent diabetes mellitus" OR "T2DM" OR "T2D")

Web of Science:

TS=("glucagon-like peptide-1/glucagon dual agonist" OR "twincretin" OR "cotadutide" OR "MEDI0382") AND TS=("type 2 diabetes" OR "type 2 diabetes mellitus" OR "non-insulin dependent diabetes mellitus" OR "T2DM" OR "T2D")

Supplementary Table 1 Characteristics of the trials and trial participants excluded from this meta-analysis

Trial	ID	Trial registration	Type	of	Major inclusion	Trial arms	Reason	for	Main findings
[Ref.];		number	study		criteria	(sample size, n)	exclusion		
Ambery	et	NCT02394314	Phase 1 RO	СТ	Healthy subjects	MEDI0382 (n =	Study co	onducted	(1) TEAEs occurred more frequently with
al[27]					(aged 18-45	36); placebo (<i>n</i> =	among	healthy	MEDI0382 vs. placebo, which was mostly
					years), BMI 22-	12)	subjects		due to an increased occurrence at
					30 kg/m², body				MEDI0382 doses \geq 150 µg; (2) All TEAEs
					weight ≥70 kg				were mild or moderate in severity; (3)
									The most common TEAEs were
									vomiting, nausea and dizziness. There
									appeared to be a dose-dependent
									increase in heart rate with MEDI0382
									treatment; (4) MEDI0382 showed linear
									pharmacokinetic profile (time to
									maximum plasma concentration: 4.50-
									9.00 h; elimination half-life: 9.54-12.07
									hours); and (5) No immunogenicity was
									observed in the study.
Bosch	et	NCT02548585	Multiple		Overweight or	Cotadutide	Multiple		The 4GI quantitative systems
al[28]			ascending	т Э	obese		ascending	dose	pharmacology model was able to predict

	dose/phase	individuals with	(n = 25); placebo	study using four	the clinical effects of cotadutide on
	2a study	T2D	(n = 26)	glucose dynamics	glucose, insulin, GLP-1, glucagon and
				systems model, in	GIP given known in vitro potency
				combination with	
				clinical data from a	
				Phase 2a study	
Klein et al[29] NCT03235375	Single-Dose,	Individuals 18-	Cotadutide 100	Single-dose, phase	The PK and tolerability of cotadutide are
	Phase 1,	85 years of age,	$\mu g (n = 37)$	1, bridging study;	unaffected by renal function and that
	Bridging	with a BMI of		all study subjects	dose adjustments may not be required in
	Study	$17-40 kg/m^2$		did not have	individuals with renal impairment
		and varying		diabetes	
		degrees of renal			
		function			
Shankar et NCT04019561	Phase 2 RCT	Adults with	Cotadutide 300	Included patients	(1) Dose- and time-dependent
al[30]		biopsy-proven,	$\mu g (n = 25);$	with or without	improvements in HFF, ALT, and AST,
		noncirrhotic	Cotadutide 600	T2D	markers of liver health, and metabolic
		MASH with	$\mu g (n = 25);$		parameters were observed with
		fibrosis; 55% had	Placebo ($n = 24$)		significant improvements after 19 weeks
		T2D			with 600 μg (least squares MD vs placebo,
					95%CI for absolute HFF: -5.0% (8.5 to -

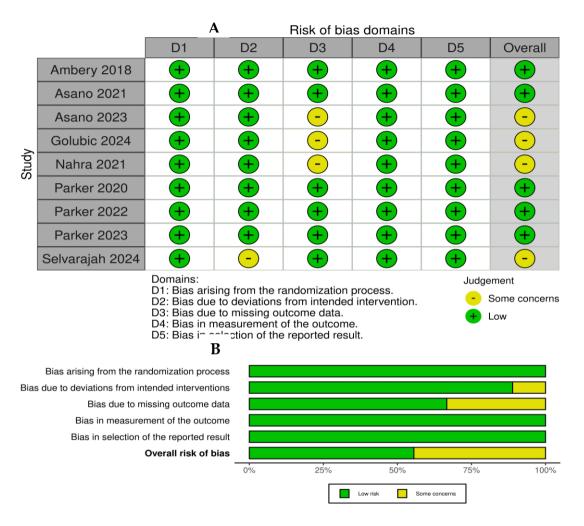
1.5); ALT: -23.5 U/L (-47.1 to -1.8); AST: -16.8 U/L (-33.0 to -0.8); (2) Least squares MD vs placebo, 95%C] for absolute differences in body weight was -0.44 kg (-2.78 to 1.90) for cotadutide 300 µg and -2.36 kg(-4.71 to -0.002) cotadutide 600 µg; (3) Least squares MD vs placebo, (95% CI) for absolute differences in HbA1c was -0.33% (-0.97 to 0.3) for cotadutide 300 μg and -0.44% (-1.05 to 0.18) cotadutide 600 µg; and (4) Incidences of any grade TEAEs were 91.7%, 76.9%, and 37.5% with cotadutide 600 µg, 300 µg, and placebo, respectively.

with Cotadutide 100 Substudy of the (1) A significant relationship was Yu et al[31] NCT04515849 PK/PD Patients modelling μ g (n = 52); CKD and T2D of

included study by identified between cotadutide exposure and PD biomarkers of UACR, UALB and

cotadutide	Cotadutide 300	Selvarajah	et al.	body weight; (2) The models described
effect	$\mu g (n = 48);$	(2024)		the data adequately; greater changes in
	Cotadutide 600			PD responses were observed with higher
	μ g ($n = 51$);			cotadutide doses; (3) Baseline mean
	Semaglutide 1			blood pressure and baseline UALB were
	mg (n = 45);			found to affect the reductions in UACR
	Placebo ($n = 51$)			and UALB, respectively; and (4) Model-
				predicted relative change from placebo in
				UACR, UALB and body weight after 26
				weeks of 600 µg cotadutide treatment
				were 45.6% (52.4%, 38.7%), 47.2%
				(56.0%, 39.9%) and 5.3% (7.6%, 4.1%),
				respectively.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CI: Confidence interval; CKD: Chronic kidney disease; HbA1c: Glycated hemoglobin; HFF: Hepatic fat fraction; MASH: Metabolic dysfunction-associated steatohepatitis; MD: Mean difference; PK/PD: Pharmacokinetic-pharmacodynamic; RCT: Randomized controlled trial; T2D: Type 2 diabetes; TEAE: Treatment-emergent adverse events



Supplementary Figure 1 Risk of bias A: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study using RoB2; B: Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

Supplementary Table 2 Summary of findings table

Outcomes	Anticipated absolute effects ¹ (95%	No. of participants	Certainty of the			
	Risk with placebo	Risk with cotadutide	(studies)	evidence (GRADE)		
HbA1c - cotadutide 100 μg	The mean change in HbA1c was -	MD 0.77 lowe	r 346 (3 RCTs)	0000		
	0.34%	(1.06 lower to 0.47 lower)		Very low ^{a,b,c}		
HbA1c - cotadutide 200 μg	The mean change in HbA1c was -	MD 0.68 lowe	r 450 (3 RCTs)	Θ		
	0.44%	(1.12 lower to 0.23 lower)		Very low ^{b,c,d}		
HbA1c - cotadutide 300 μg	The mean change in HbA1c was -	MD 0.67 lowe	r 579 (5 RCTs)	$\Theta\Theta\bigcirc\bigcirc$		
	0.31%	(0.79 lower to 0.56 lower)		Low ^{c,e}		
HbA1c - cotadutide 600 μg	The mean change in HbA1c was -	MD 0.69 lowe	r 118 (2 RCTs)	Θ		
	0.24%	(0.97 lower to 0.41 lower)		Very low ^{b,c}		
Precent body weight -	The mean change in percent body	MD 1.74 lowe	r 346 (3 RCTs)	Θ		
cotadutide 100 μg	weight was -1.13%	(3.23 lower to 0.25 lower)		Very low ^{b,c}		
Precent body weight -	The mean change in percent body	MD 2.56 lowe	r 418 (3 RCTs)	Θ		
cotadutide 200 μg	ide 200 μ g weight was -0.73% (3.37 lower to 1.75 lower)					
Precent body weight -	The mean change in percent body	MD 3.49 lowe	r 579 (5 RCTs)	Θ		
cotadutide 300 μg	weight was -0.98%	(4.14 lower to 2.84 lower)		Very low ^{b,c}		
Precent body weight -	The mean change in percent body	MD 5.45 lowe	r 118 (2 RCTs)	\oplus		
cotadutide 600 μg	weight was -2.16%	(7.17 lower to 3.73 lower)		Very low ^{b,c}		

^aModerate heterogeneity among the studies is present.

bSmall number of studies with relatively few patients and a wide CI around the estimate of the effect.

^cSmall number of early-phase, sponsor-funded RCTs.

dHigh heterogeneity among the studies is present.

eSmall number of studies with relatively few patients.

¹The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

GRADE working group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. CI: confidence interval; MD: mean difference.

	Cota	dutide 300	μg		Placebo			Mean difference	Mean diff	erence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Randon	ո, 95% CI
2.1.1 <10 weeks										
Asano 2021	-0.9	0.496586	15	-0.14	0.497314	16	10.8%	-0.76 [-1.11 , -0.41]		
Parker 2020	-0.67	0.358992	26	-0.07	0.339239	13	25.0%	-0.60 [-0.83 , -0.37]	-	
Parker 2022	-0.65	0.362482	21	0.01	0.34187	20	28.5%	-0.66 [-0.88 , -0.44]	-	
Subtotal (Wald ^a)			62			49	64.3%	-0.65 [-0.80 , -0.51]	•	
Test for overall effect:	Z = 8.92 (F	o < 0.00001	L)						Ť	
Heterogeneity: Tau² (D)Lb) = 0.00	; Chi² = 0.5	7, df = 2 (P = 0.75	; I ² = 0%					
2.1.2 ≥10 weeks										
2.1.2 210 Weeks Nahra 2021	-1 10	1.178077	256	-0.45	1.094849	112	21.4%	-0.74 [-0.99 , -0.49]		
Selvarajah 2024	-0.92	0.77	49		0.785557	51				
Subtotal (Walda)	-0.92	0.77	305	-0.25	0.765557	163				
` '	7 - 7 04 (1	2 < 0.00001				103	35.7%	-0.71 [-0.90 , -0.52]	•	
Test for overall effect:	•		,	D - 0.70\	. 12 — 00/					
Heterogeneity: Tau² (D	(0.00) = 0.00	; Cni² = 0.1	2, ai = 1 (P = 0.73	; 12 = 0%					
Total (Wald ^a)			367			212	100.0%	-0.67 [-0.79 , -0.56]	•	
Test for overall effect:	Z = 11.48	(P < 0.0000	1)						-1 -0.5 0	0.5 1
Test for subgroup diffe		•	,	0.63), I ²	= 0%			Favors Cota	adutide 300 µg	Favors PC
Heterogeneity: Tau ² (D			`	,,					. 3	

Supplementary Figure 2 Forest plot highlighting the mean difference in the changes from the baseline in glycated hemoglobin between the cotadutide 300 μ g and placebo groups: subgroup analysis according to the duration of trials (< 10 weeks versus \geq 10 weeks).

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

Study or Subgroup	C Mean [%]	otadutide SD [%]	Total	Mean [%]	ACG SD [%]	Total	Weight	Mean difference IV, Random, 95% CI [%]	Mean difference IV, Random, 95% CI [%]
3.1.1 Cotadutide 100) ua								
Nahra 2021		1.133949	100	-1.17	1.031892	110	49.5%	0.14 [-0.15 , 0.43	31
Selvarajah 2024	-0.92	0.793221	52		0.67082	45	50.5%	-	-
Subtotal (Walda)			152			155	100.0%	-	-
Test for overall effect:	Z = 1.99 (P	= 0.05)						- '	
Heterogeneity: Tau ² (I			df = 1 (P	= 0.51); I ² =	: 0%				
3.1.2 Cotadutide 300) µg								
Nahra 2021	-1.19	1.178077	256	-1.17	1.031892	110	53.9%	-0.02 [-0.26 , 0.22	2] —
Selvarajah 2024	-0.92	0.77	49	-1.2	0.67082	45	46.1%	0.28 [-0.01 , 0.57	7]
Subtotal (Walda)			305			155	100.0%	0.12 [-0.17 , 0.41	.]
Test for overall effect:	Z = 0.79 (P = 0.79)	= 0.43)							
Heterogeneity: Tau ² (I	DLb) = 0.03; (df = 1 (P	= 0.12); I ² =	59%				
	•		•	,					
Test for subgroup diffe	erences: Chi ²	$r^2 = 0.25, df = 0.25$	= 1 (P = 0	0.61), I ² = 0%	6				-1 -0.5 0 0.5
- •			-	-				1	Favors Cotadutide Favors AC

Supplementary Figure 3 Forest plot highlighting the mean difference in the changes from the baseline in glycated hemoglobin between the cotadutide and active control groups.

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

	Cota	dutide 300	μg		Placebo			Mean difference	Mean dif	ference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Randon	n, 95% CI
2.2.1 <10 weeks										
Asano 2021	-3.34	2.257208	15	-0.82	2.345821	16	16.1%	-2.52 [-4.14 , -0.90]		
Parker 2020	-3.41	2.389154	26	-0.08	2.093352	13	19.7%	-3.33 [-4.79 , -1.87]		
Parker 2022	-3.69	1.889302	21	-0.21	1.784133	20	33.4%	-3.48 [-4.60 , -2.36]	-	
Subtotal (Walda)			62			49	69.2%	-3.21 [-4.00 , -2.43]	•	
Test for overall effect:	Z = 8.07 (F	o < 0.00001	.)						•	
Heterogeneity: Tau ² (D	DLb) = 0.00	; $Chi^2 = 0.9$	4, df = 2 (P = 0.62)	$I^2 = 0\%$					
2.2.2 ≥10 weeks										
Nahra 2021	-5.02	6.17475	256	-0.68	5.848095	112	24.2%	-4.34 [-5.66 , -3.02]		
Selvarajah 2024	-5.45	6.44	49	-2.23	6.427286	51	6.6%	-3.22 [-5.74 , -0.70]		
Subtotal (Walda)			305			163	30.8%	-4.10 [-5.27 , -2.93]	•	
Test for overall effect:	Z = 6.86 (I	P < 0.00001	.)						Ť	
Heterogeneity: Tau ² (D	DLb) = 0.00	; Chi ² = 0.5	9, df = 1 (P = 0.44)	$; I^2 = 0\%$					
Total (Wald ^a)			367			212	100.0%	-3.49 [-4.14 , -2.84]	•	
Test for overall effect:	Z = 10.52	(P < 0.0000	01)					⊢ -10) -5 0	5 10
Test for subgroup diffe		•	•	0.22), I ²	= 34.2%			Favors Cotad	, ,	Favors PCG
Heterogeneity: Tau ² (C			•						. 5	

Supplementary Figure 4 Forest plot highlighting the mean difference in the percent changes from the baseline in body weight between the cotadutide 300 μ g and placebo groups: subgroup analysis according to the duration of trials (< 10 weeks versus \geq 10 weeks).

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

	С	otadutide			ACG			Mean difference	Mean difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
3.2.1 Cotadutide 100) µg								
Nahra 2021	-3.7	6.072925	100	-3.33	5.397591	110	51.8%	-0.37 [-1.93 , 1.19]	
Selvarajah 2024	-2.6	6.417881	52	-7	5.366563	45	48.2%	4.40 [2.05 , 6.75]	
Subtotal (Walda)			152			155	100.0%	1.93 [-2.74 , 6.60]	
Test for overall effect:	Z = 0.81 (P = 0.81)	= 0.42)							
Heterogeneity: Tau² (I	DLb) = 10.34;	$Chi^2 = 11.0$	01, df = 1	(P = 0.0009)); I ² = 91%				
3.2.2 Cotadutide 300) µg								
Nahra 2021	-5.02	6.17475	256	-3.33	5.397591	110	55.1%	-1.69 [-2.95 , -0.43]	-
Selvarajah 2024	-5.45	6.44	49	-7	5.366563	45	44.9%	1.55 [-0.84 , 3.94]	 •
Subtotal (Walda)			305			155	100.0%	-0.24 [-3.39 , 2.92]	
Test for overall effect:	Z = 0.15 (P	= 0.88)							
Heterogeneity: Tau² (I	DL ^b) = 4.30; ($Chi^2 = 5.52,$	df = 1 (P	= 0.02); I ² =	82%				
, ,	,		`	,					
Test for subgroup diffe	erences: Chi ²	² = 0.57, df	= 1 (P = 0	0.45), $I^2 = 0$	6				-10 -5 0 5
			•	•				F	avors Cotadutide Favors ACC

Supplementary Figure 5 Forest plot highlighting the mean difference in the percent changes from the baseline in body weight between the cotadutide and active control groups.

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

	c	Cotadutide			PCG			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.3.1 Cotadutide 100	μg								
Asano 2021	-3.17	1.273065	15	-0.02	1.276127	16	32.8%	-3.15 [-4.05 , -2.25]	
Nahra 2021	-1.7	2.2049	100	-0.8	2.189698	112	35.5%	-0.90 [-1.49 , -0.31]	-
Selvarajah 2024	-1.78	2.595997	52	-0.72	2.642329	51	31.7%	-1.06 [-2.07, -0.05]	
Subtotal (Waldª)			167			179	100.0%	-1.69 [-3.10 , -0.28]	
Test for overall effect:	Z = 2.35 (F	P = 0.02)							
Heterogeneity: Tau² ([DL ^b) = 1.37	; Chi ² = 17.	63, df = 2	(P = 0.00)	01); $I^2 = 89$	%			
1.3.2 Cotadutide 200	μg								
Ambery 2018	-2.8	0.902171	22	-1.1	0.84791	25	27.5%	-1.70 [-2.20 , -1.20]	-
Asano 2021	-3.39	1.589074	15	-0.02	1.276127	16	17.3%	-3.37 [-4.39 , -2.35]	
Golubic 2024	-2.1	0.55086	12	-0.7	0.540631	7	27.4%	-1.40 [-1.91 , -0.89]	-
Nahra 2021	-2.21	2.234284	256	-0.8	2.189698	112	27.8%	-1.41 [-1.90 , -0.92]	-
Subtotal (Waldª)			305			160	100.0%	-1.83 [-2.43 , -1.22]	•
Test for overall effect:	Z = 5.93 (F	P < 0.00001	L)						•
Heterogeneity: Tau² ([DL ^b) = 0.28	; Chi ² = 12.	84, df = 3	(P = 0.00)	5); I ² = 77%	ó			
1.3.3 Cotadutide 300	μg								
Asano 2021	-3.08	1.480728	15	-0.02	1.276127	16	12.4%	-3.06 [-4.04 , -2.08]	
Nahra 2021	-2.23	2.234284	256	-0.8	2.189698	112	18.5%	-1.43 [-1.92 , -0.94]	-
Parker 2020	-1.96	1.015081	26	-0.13	0.959798	13	16.4%	-1.83 [-2.48 , -1.18]	
Parker 2022	-1.09	1.689388	21	0.03	1.600378	20	12.1%	-1.12 [-2.13 , -0.11]	
Parker 2023-A	-2.47	2.24	10	-0.11	0.47	9	8.3%	-2.36 [-3.78 , -0.94]	
Parker 2023-B	-2.23	0.455333	9	0.17	0.1	11	20.5%	-2.40 [-2.70 , -2.10]	•
Selvarajah 2024	-1.76	2.59	49	-0.72	2.642329	51	11.9%	-1.04 [-2.07 , -0.01]	-
Subtotal (Walda)			386			232	100.0%	-1.89 [-2.41 , -1.37]	◆
Test for overall effect:	Z = 7.14 (F	P < 0.00001	L)						•
Heterogeneity: Tau ² ([DL^{b}) = 0.32	; Chi ² = 23.	02, df = 6	(P = 0.00	08); I ² = 74	%			
Test for subgroup diffe	erences: C	$hi^2 = 0.08, c$	df = 2 (P =	0.96), I ² :	= 0%				-4 -2 0 2
								Fav	ors Cotadutide Favors I
Footnotes									

Supplementary Figure 6 Forest plot highlighting the mean difference in the changes from the baseline in fasting plasma glucose between the cotadutide and placebo groups

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

	Cota	dutide 300	μg		ACG			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
Nahra 2021	-2.23	2.234284	256	-2.19	2.196079	110	42.2%	-0.04 [-0.53 , 0.4	5]
Parker 2023-B	-2.23	0.455333	9	-2.05	0.482277	10	57.8%	-0.18 [-0.60 , 0.24	1] -
Total (Wald ^a)			265			120	100.0%	-0.12 [-0.44 , 0.20	D] •
Test for overall effect:	Z = 0.74 (P = 0.46)							-2 -1 0 1 2 Favors Cotadutide Favors ACG

Heterogeneity: Tau 2 (DL b) = 0.00; Chi 2 = 0.18, df = 1 (P = 0.67); I 2 = 0%

Footnotes

^aCI calculated by Wald-type method.

Supplementary Figure 7 Forest plot highlighting the mean difference in the changes from the baseline in fasting plasma glucose between the cotadutide and active control groups.

^bTau² calculated by DerSimonian and Laird method.

Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 1.4.1 Cotadutide 200 µg 1.4.1 Cotadutide 200 µg -3.84 1.732159 25 -1.7 1.720686 26 45.0% -2.14 [-3.09, -1.19]		C	Cotadutide			PCG			Mean difference	Mean differen	ce
Ambery 2018	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95%	6 CI
Golubic 2024 -3.8 1.337804 12 -1.3 1.297514 7 27.0% -2.50 [-3.72 , -1.28]	1.4.1 Cotadutide 200	μg									
Nahra 2021 -3.09 5.484153 256 -0.94 5.36743 112 28.1% -2.15 [-3.35 , -0.95] Subtotal (Walda) 293 145 100.0% -2.24 [-2.88 , -1.60] Test for overall effect: Z = 6.91 (P < 0.00001) Heterogeneity: Tau² (DLb) = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0% 1.4.2 Cotadutide 300 μg Nahra 2021 -4.35 5.484153 256 -0.94 5.36743 112 22.1% -3.41 [-4.61 , -2.21]	Ambery 2018	-3.84	1.732159	25	-1.7	1.720686	26	45.0%	-2.14 [-3.09 , -1.19]	-	
Subtotal (Walda) Test for overall effect: Z = 6.91 (P < 0.00001) Heterogeneity: Tau² (DLb) = 0.00; Chi² = 0.24, df = 2 (P = 0.89); ² = 0% 1.4.2 Cotadutide 300 μg Nahra 2021	Golubic 2024	-3.8	1.337804	12	-1.3	1.297514	7	27.0%	-2.50 [-3.72 , -1.28]		
Test for overall effect: Z = 6.91 (P < 0.00001) Heterogeneity: Tau² (DLb) = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0% 1.4.2 Cotadutide 300 µg Nahra 2021	Nahra 2021	-3.09	5.484153	256	-0.94	5.36743	112	28.1%	-2.15 [-3.35 , -0.95]		
Heterogeneity: Tau² (DLb) = 0.00; Chi² = 0.24, df = 2 (P = 0.89); l² = 0% 1.4.2 Cotadutide 300 μg Nahra 2021	Subtotal (Walda)			293			145	100.0%	-2.24 [-2.88 , -1.60]	•	
1.4.2 Cotadutide 300 μg Nahra 2021 -4.35 5.484153 256 -0.94 5.36743 112 22.1% -3.41 [-4.61 , -2.21] —— Parker 2022 -3.41 1.735522 21 -0.13 1.645249 20 26.5% -3.28 [-4.31 , -2.25] —— Parker 2023-A -4.03 1.383925 10 -0.27 1.16 9 23.5% -3.76 [-4.90 , -2.62] —— Parker 2023-B -2.5 1.092799 9 -0.33 1.16 11 27.9% -2.17 [-3.16 , -1.18] —— Subtotal (Wald³)	Test for overall effect:	Z = 6.91 (I	o < 0.00001	.)						•	
Nahra 2021 -4.35 5.484153 256 -0.94 5.36743 112 22.1% -3.41 [-4.61 , -2.21] ————————————————————————————————————	Heterogeneity: Tau² (D	DLb) = 0.00	; $Chi^2 = 0.2$	4, df = 2 (P = 0.89	$I^2 = 0\%$					
Nahra 2021 -4.35 5.484153 256 -0.94 5.36743 112 22.1% -3.41 [-4.61 , -2.21] ————————————————————————————————————	1.4.2 Cotadutide 300	μg									
Parker 2023-A -4.03 1.383925 10 -0.27 1.16 9 23.5% -3.76 [-4.90 , -2.62] ————————————————————————————————————	Nahra 2021	-4.35	5.484153	256	-0.94	5.36743	112	22.1%	-3.41 [-4.61 , -2.21]		
Parker 2023-B -2.5 1.092799 9 -0.33 1.16 11 27.9% -2.17 [-3.16 , -1.18]	Parker 2022	-3.41	1.735522	21	-0.13	1.645249	20	26.5%	-3.28 [-4.31 , -2.25]		
Subtotal (Walda) 296 152 100.0% -3.11 [-3.82 , -2.41] Test for overall effect: Z = 8.66 (P < 0.00001)	Parker 2023-A	-4.03	1.383925	10	-0.27	1.16	9	23.5%	-3.76 [-4.90 , -2.62]		
Test for overall effect: $Z = 8.66 (P < 0.00001)$	Parker 2023-B	-2.5	1.092799	9	-0.33	1.16	11	27.9%	-2.17 [-3.16 , -1.18]		
· · · · · ·	Subtotal (Walda)			296			152	100.0%	-3.11 [-3.82 , -2.41]		
	Test for overall effect:	Z = 8.66 (I	o < 0.00001	_)					- · · · -	•	
Heterogeneity: Tau ² (DL ^b) = 0.21; Chi ² = 5.04, df = 3 (P = 0.17); $I^2 = 40\%$	Heterogeneity: Tau ² (D	DL ^b) = 0.21	; Chi ² = 5.0	4, df = 3 (P = 0.17)	; I ² = 40%					
	lest for subgroup diffe	erences: C	$ni^2 = 3.25, 0$	IT = 1 (P =	(0.07), l ²	= 69.2%			F	-4 -2 0 :	2
,									Fa	vors Cotadutide Fa\	ors F

Supplementary Figure 8 Forest plot highlighting the mean difference in the absolute changes from the baseline in body weight between the cotadutide and placebo groups.

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

	Cota	dutide 300	μg		ACG			Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Nahra 2021	-4.35	5.484153	256	-2.94	5.397591	110	71.9%	-1.41 [-2.62 , -0.20)] — = —
Parker 2023-B	-2.5	1.092799	9	-2.8	3.91413	10	28.1%	0.30 [-2.23 , 2.83	· · · · · · · · · · · · · · · · · · ·
Total (Wald ^a)			265			120	100.0%	-0.93 [-2.44 , 0.58	
Test for overall effect:	Z = 1.21 (I	P = 0.23)						ı	-4 -2 0 2 4 Favors Cotadutide Favors PCG

Heterogeneity: Tau^2 (DL^b) = 0.44; Chi² = 1.43, df = 1 (P = 0.23); I^2 = 30%

Footnotes

^aCI calculated by Wald-type method.

Supplementary Figure 9 Forest plot highlighting the mean difference in the absolute changes from the baseline in body weight between the cotadutide and active control groups.

^bTau² calculated by DerSimonian and Laird method.