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

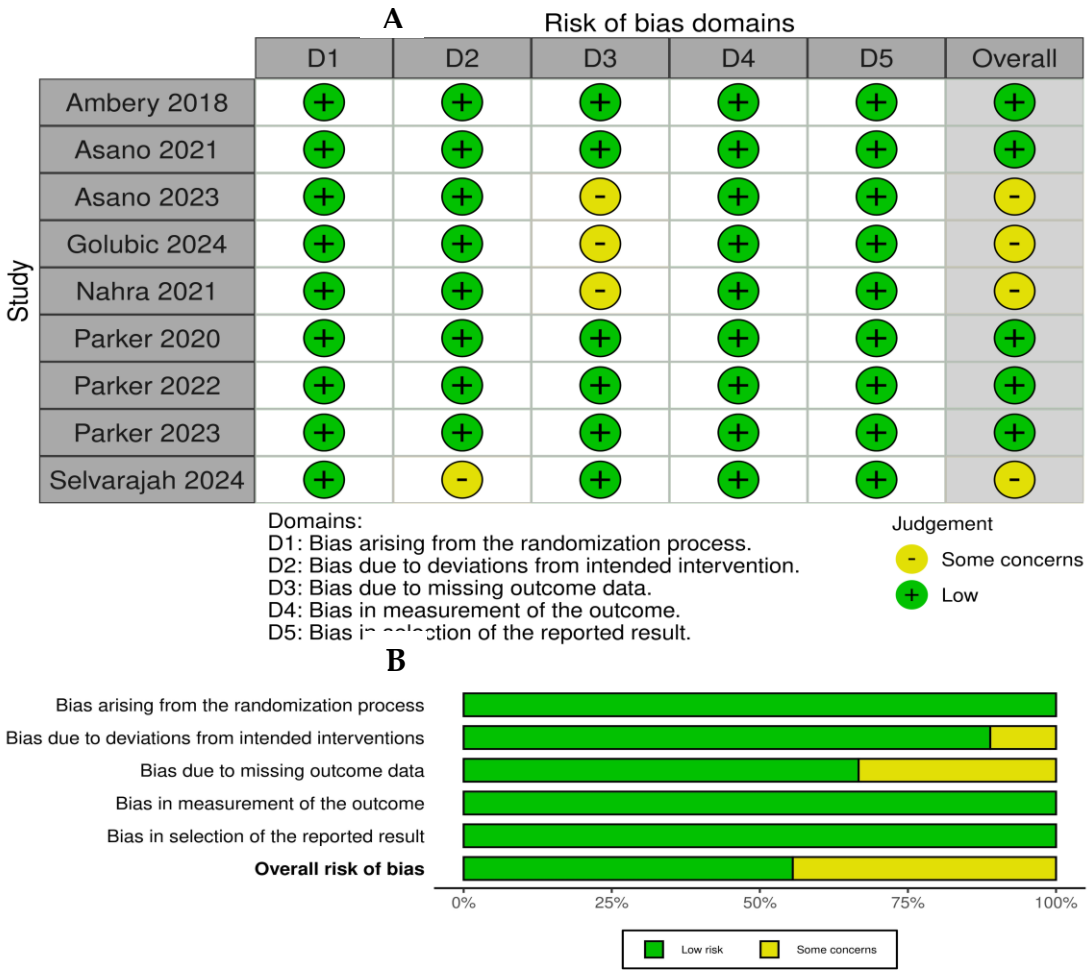
Trial ID [Ref.];	Trial registration number	Type of study	Major inclusion criteria	Trial arms (sample size, *n*)	Reason for exclusion	Main findings
Ambery *et al*[27]	NCT02394314	Phase 1 RCT	Healthy subjects (aged 18–45 years), BMI 22-30 kg/m^2, body weight ≥70 kg	MEDI0382 (*n* = 36); placebo (*n* = 12)	Study conducted among healthy subjects	(1) TEAEs occurred more frequently with MEDI0382 vs. placebo, which was mostly due to an increased occurrence at MEDI0382 doses ≥ 150 µg; (2) All TEAEs 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 al*[28]	NCT02548585	Multiple ascending	Overweight or obese	Cotadutide	Multiple ascending dose	The 4GI quantitative systems pharmacology model was able to predict

		dose/phase 2a study	individuals with T2D	(n = 25); placebo (n = 26)	study using four glucose dynamics systems model, in combination with clinical data from a Phase 2a study	the clinical effects of cotadutide on glucose, insulin, GLP-1, glucagon and GIP given known in vitro potency
Klein *et al*[29]	NCT03235375	Single-Dose, Phase 1, Bridging Study	Individuals 18–85 years of age, with a BMI of 17–40 kg/m^2 and varying degrees of renal function	Cotadutide 100 µg (n = 37)	Single-dose, phase 1, bridging study; all study subjects did not have diabetes	The PK and tolerability of cotadutide are unaffected by renal function and that dose adjustments may not be required in individuals with renal impairment
Shankar *et al*[30]	NCT04019561	Phase 2 RCT	Adults with biopsy-proven, noncirrhotic MASH with fibrosis; 55% had T2D	Cotadutide 300 µg (n = 25); Cotadutide 600 µg (n = 25); Placebo (n = 24)	Included patients with or without T2D	(1) Dose- and time-dependent improvements in HFF, ALT, and AST, markers of liver health, and metabolic parameters were observed with significant improvements after 19 weeks 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.
Yu *et al*[31]	NCT04515849	A PK/PD modelling of	Patients with CKD and T2D	Cotadutide 100 µg (n = 52);	Substudy of the included study by	(1) A significant relationship was identified between cotadutide exposure and PD biomarkers of UACR, UALB and

	cotadutide effect	Cotadutide 300 µg (*n* = 48); Cotadutide 600 µg (*n* = 51); Semaglutide 1 mg (*n* = 45); Placebo (*n* = 51)	Selvarajah et al. (2024)	body weight; (2) The models described the data adequately; greater changes in PD responses were observed with higher cotadutide doses; (3) Baseline mean blood pressure and baseline UALB were found to affect the reductions in UACR 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%CI)		No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with cotadutide		
HbA1c - cotadutide 100 μg	The mean change in HbA1c was -0.34%	MD 0.77 lower (1.06 lower to 0.47 lower)	346 (3 RCTs)	⊕◯◯◯ Very low[a,b,c]
HbA1c - cotadutide 200 μg	The mean change in HbA1c was -0.44%	MD 0.68 lower (1.12 lower to 0.23 lower)	450 (3 RCTs)	⊕◯◯◯ Very low[b,c,d]
HbA1c - cotadutide 300 μg	The mean change in HbA1c was -0.31%	MD 0.67 lower (0.79 lower to 0.56 lower)	579 (5 RCTs)	⊕⊕◯◯ Low[c,e]
HbA1c - cotadutide 600 μg	The mean change in HbA1c was -0.24%	MD 0.69 lower (0.97 lower to 0.41 lower)	118 (2 RCTs)	⊕◯◯◯ Very low[b,c]
Precent body weight - cotadutide 100 μg	The mean change in percent body weight was -1.13%	MD 1.74 lower (3.23 lower to 0.25 lower)	346 (3 RCTs)	⊕◯◯◯ Very low[b,c]
Precent body weight - cotadutide 200 μg	The mean change in percent body weight was -0.73%	MD 2.56 lower (3.37 lower to 1.75 lower)	418 (3 RCTs)	⊕◯◯◯ Very low[b,c]
Precent body weight - cotadutide 300 μg	The mean change in percent body weight was -0.98%	MD 3.49 lower (4.14 lower to 2.84 lower)	579 (5 RCTs)	⊕◯◯◯ Very low[b,c]
Precent body weight - cotadutide 600 μg	The mean change in percent body weight was -2.16%	MD 5.45 lower (7.17 lower to 3.73 lower)	118 (2 RCTs)	⊕◯◯◯ Very low[b,c]

[a]Moderate heterogeneity among the studies is present.

[b]Small number of studies with relatively few patients and a wide CI around the estimate of the effect.

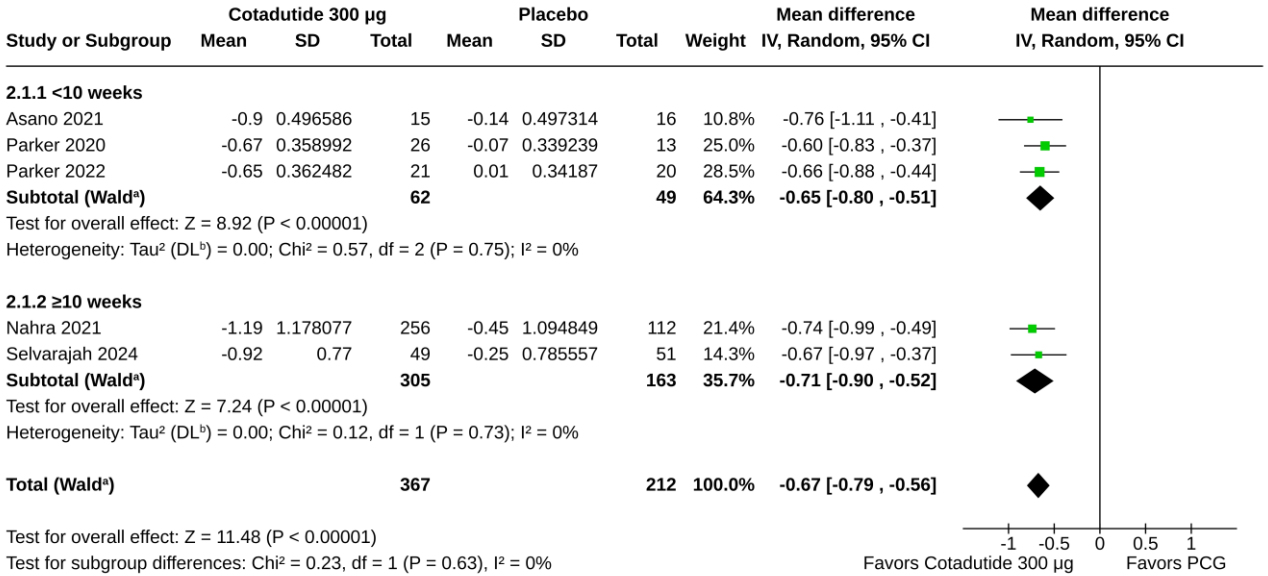
[c]Small number of early-phase, sponsor-funded RCTs.

[d]High heterogeneity among the studies is present.

[e]Small number of studies with relatively few patients.

[1]The 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.

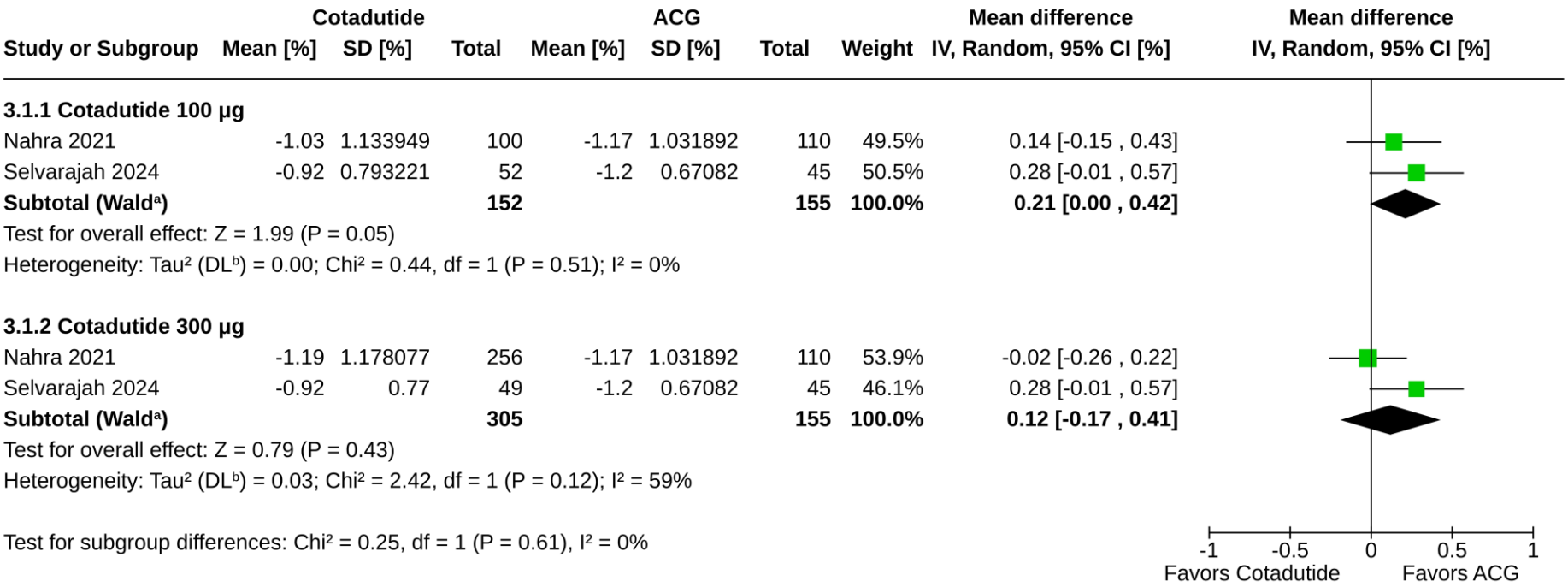


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

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

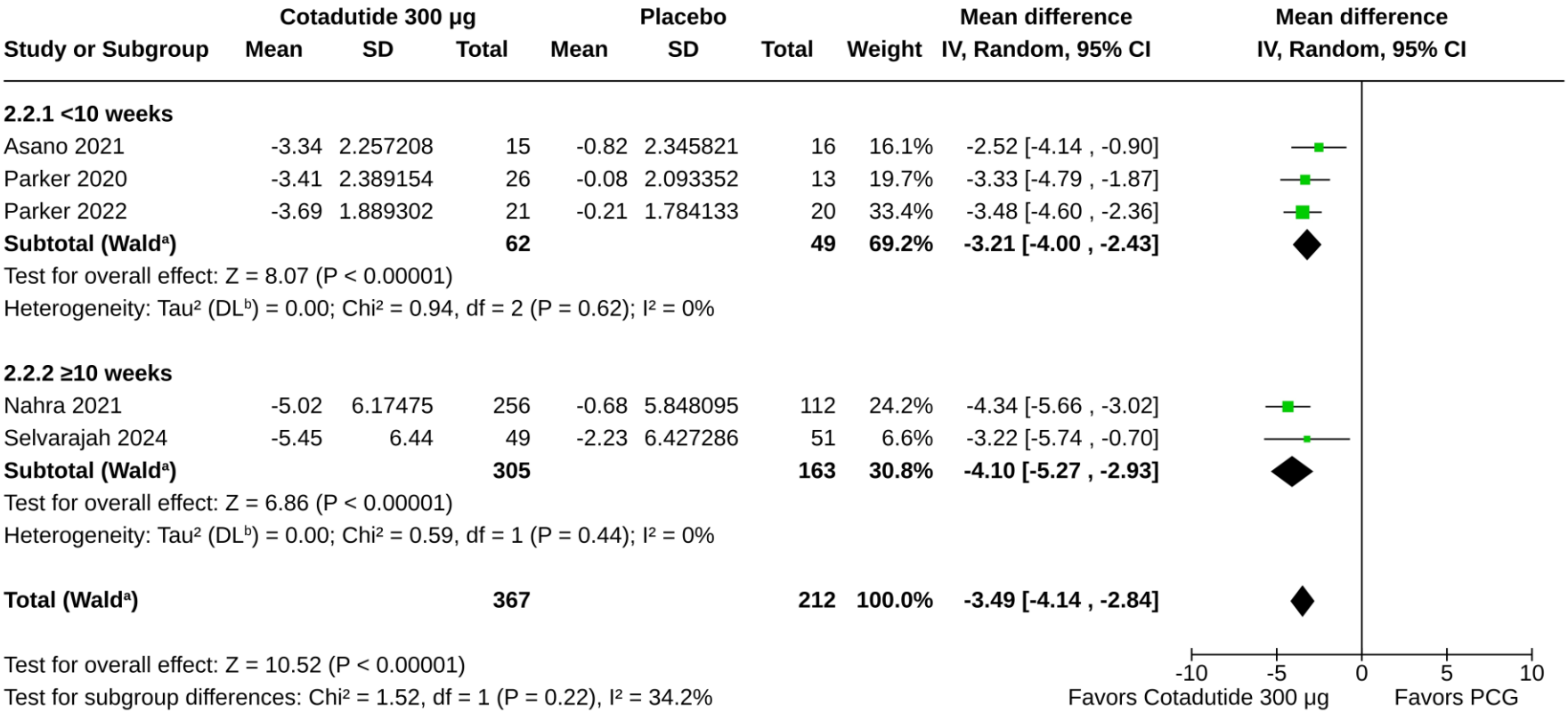


Footnotes

[a]CI calculated by Wald-type method.

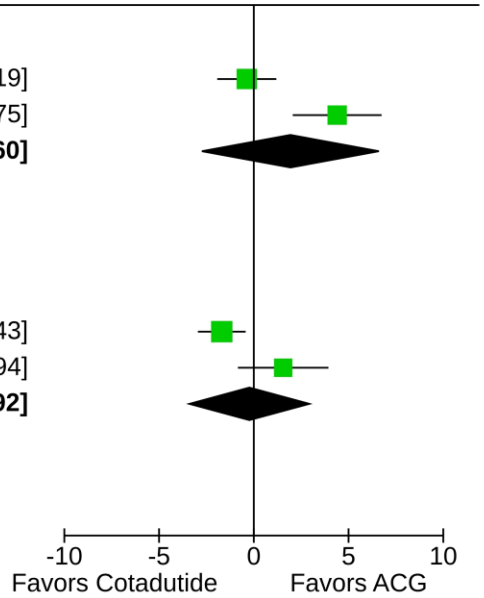
[b]Tau² calculated by DerSimonian and Laird method.

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.



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

Study or Subgroup	Cotadutide Mean [%]	Cotadutide SD [%]	Cotadutide Total	ACG Mean [%]	ACG SD [%]	ACG Total	Weight	Mean difference 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 (Wald[a])			**152**			**155**	**100.0%**	**1.93 [-2.74 , 6.60]**
Test for overall effect: Z = 0.81 (P = 0.42)								
Heterogeneity: Tau² (DL[b]) = 10.34; Chi² = 11.01, df = 1 (P = 0.0009); I² = 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 (Wald[a])			**305**			**155**	**100.0%**	**-0.24 [-3.39 , 2.92]**
Test for overall effect: Z = 0.15 (P = 0.88)								
Heterogeneity: Tau² (DL[b]) = 4.30; Chi² = 5.52, df = 1 (P = 0.02); I² = 82%								
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%								

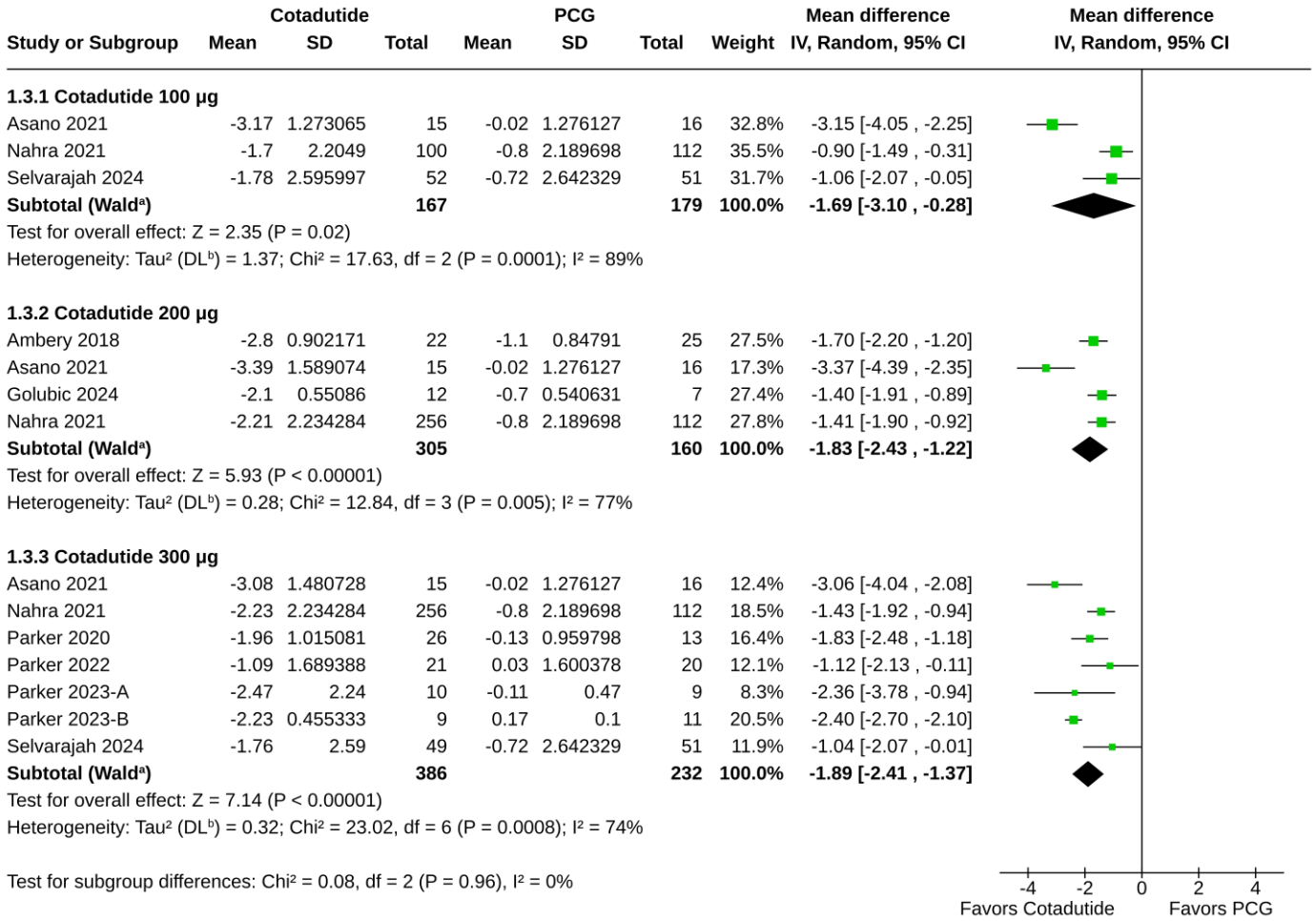


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

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.

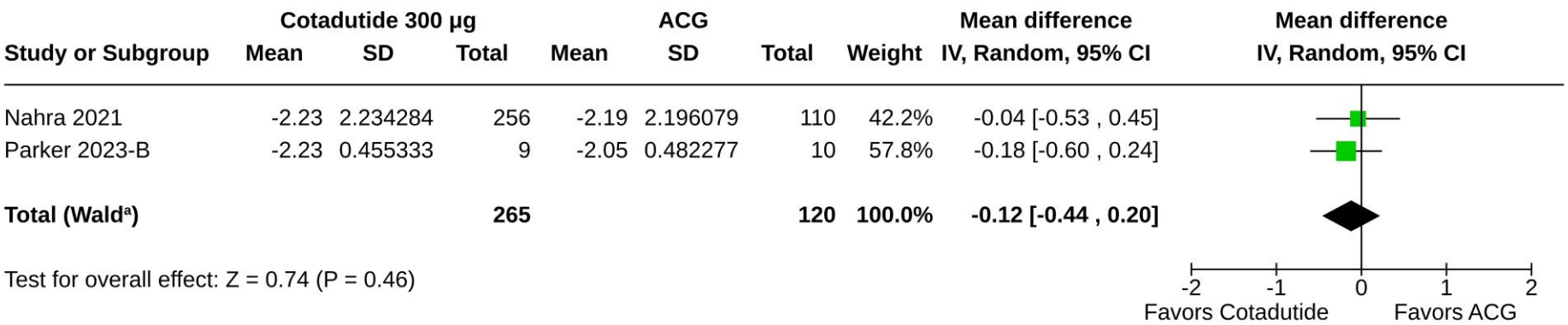


Footnotes

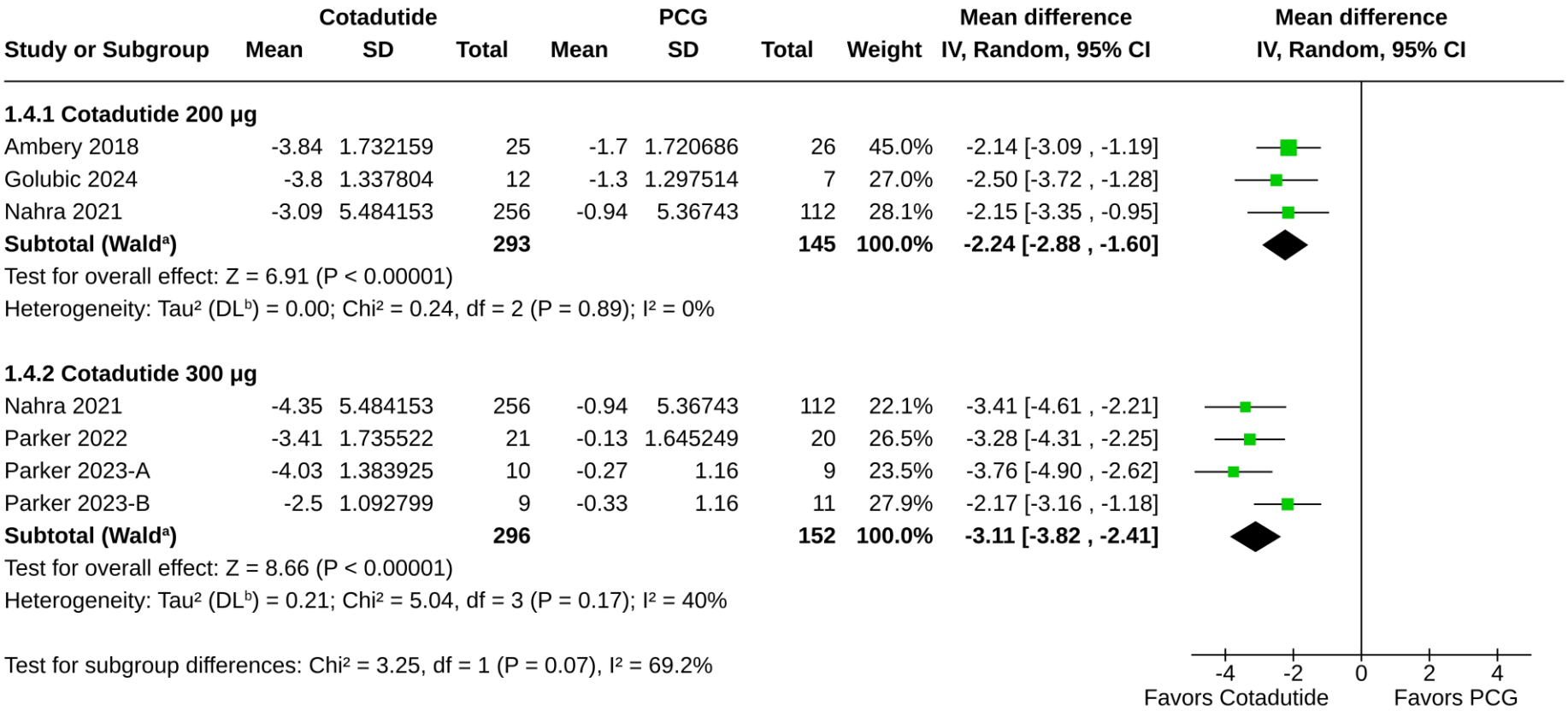
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

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



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.



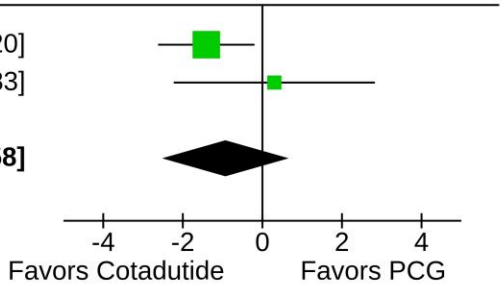
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

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.

Study or Subgroup	Cotadutide 300 µg Mean	SD	Total	ACG Mean	SD	Total	Weight	Mean difference 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 (P = 0.23)

Heterogeneity: Tau² (DL[b]) = 0.44; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird 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.