Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans.

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Abbreviated title: Glucagon-Like Peptide-1 Receptor Blockade and glucose metabolism

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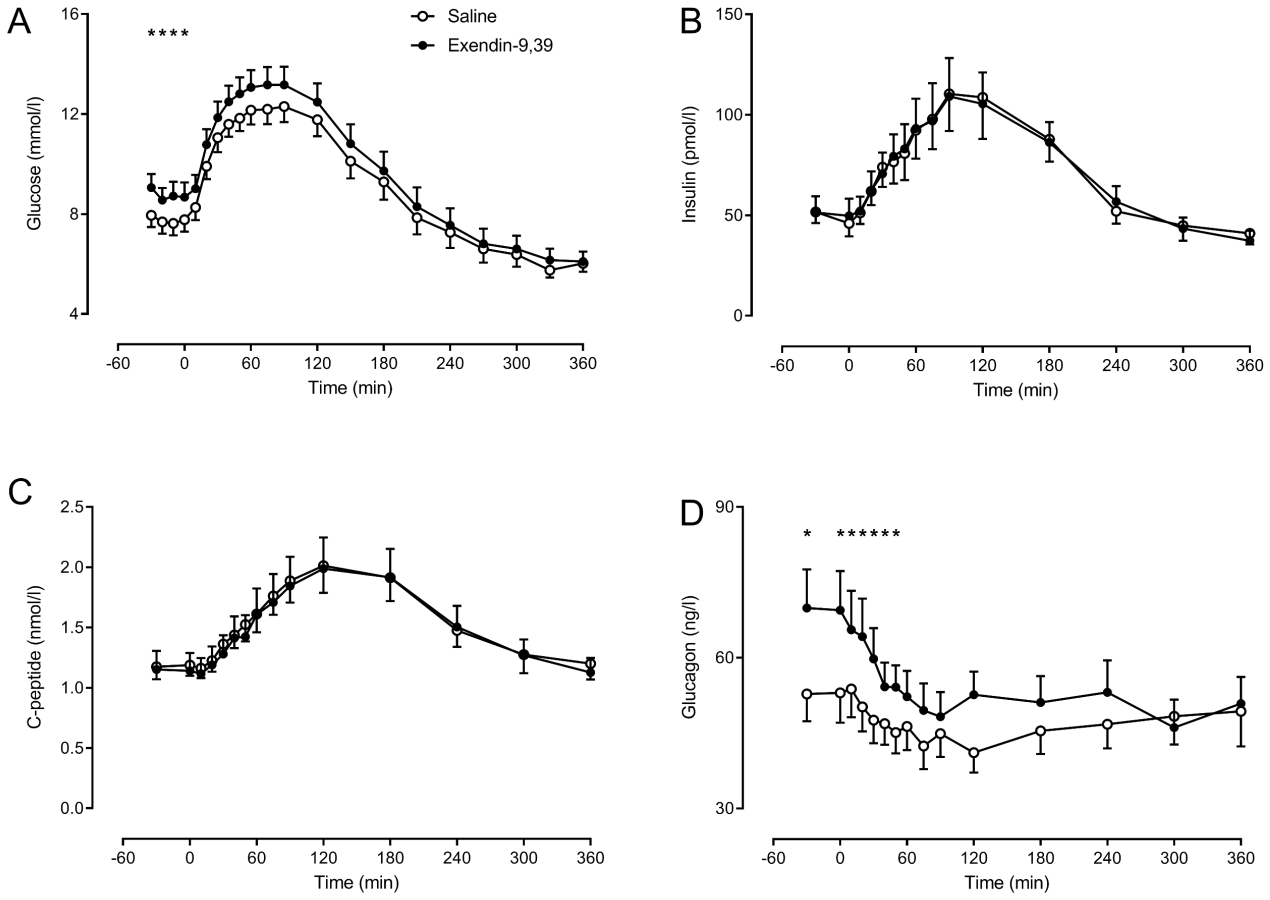
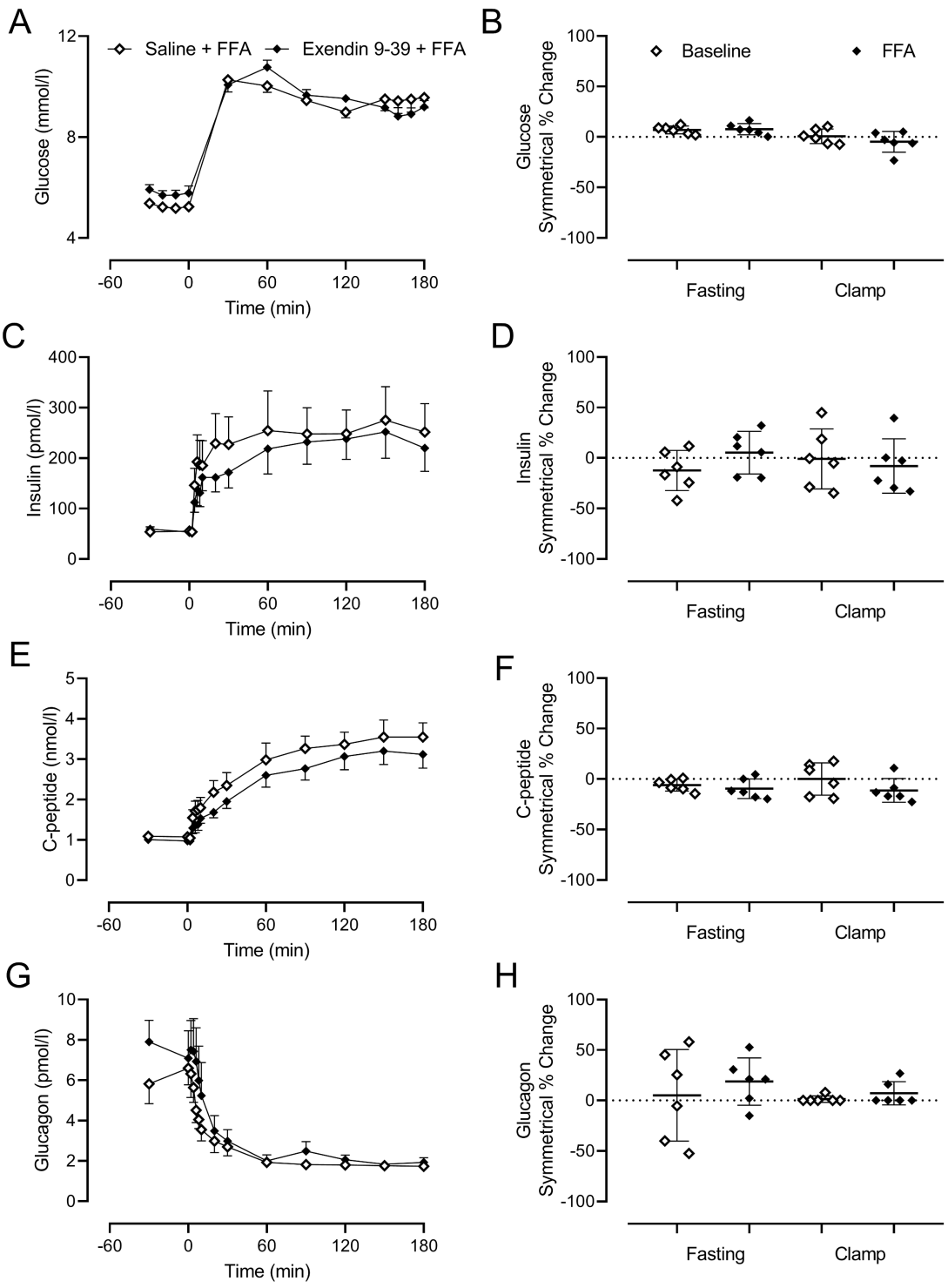
Conflict of Interest Statement

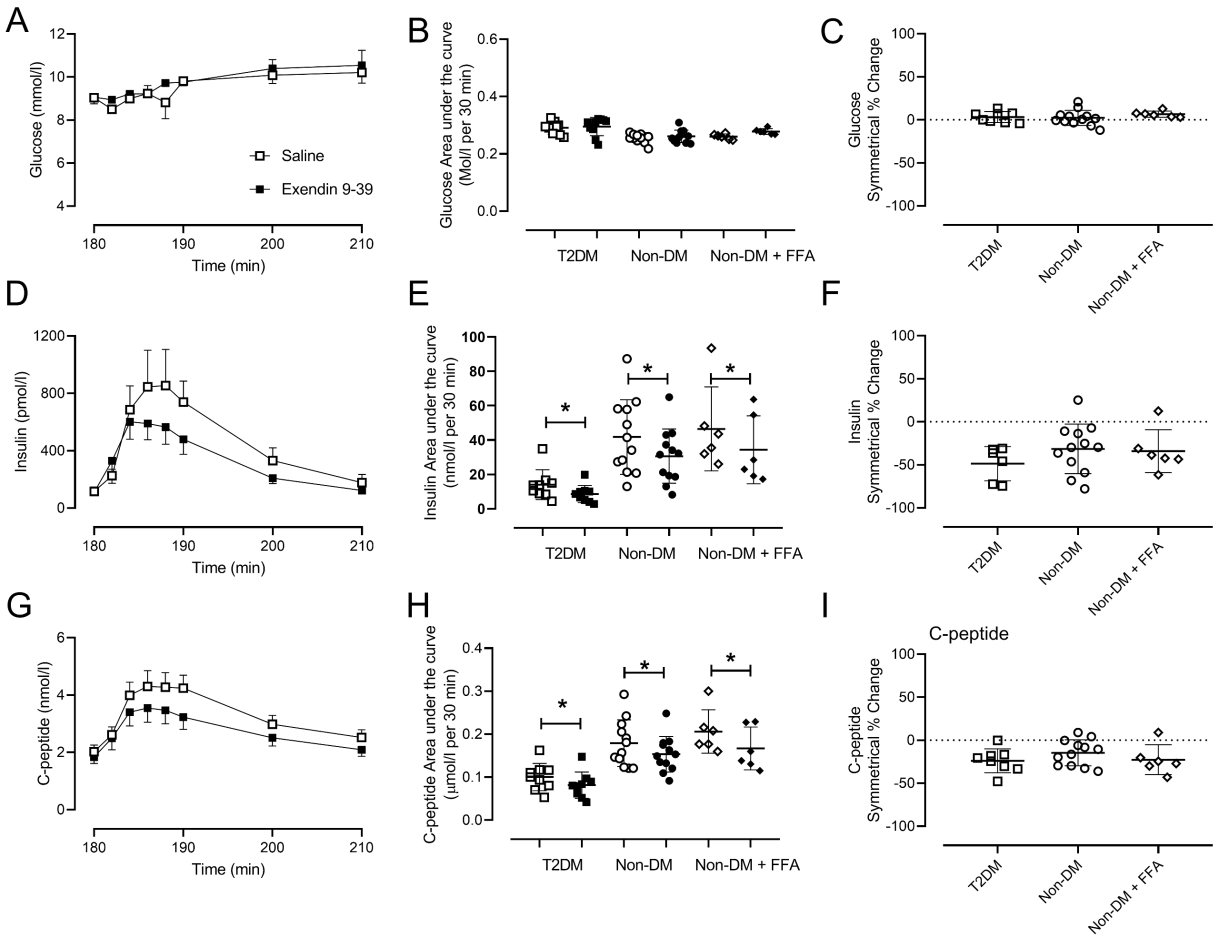
Dr. Vella is the recipient of an investigator-initiated grant from Novo Nordisk and has consulted for vTv Therapeutics, Zeeland Pharmaceuticals, Crinetics and Rezolute. None of the other authors declare conflict of interests related to this study.



Supplementary Figure 1: In an exploratory experiment performed in people with type 2 diabetes, saline (○) or exendin-9,39 (●) was infused at 300pmol/kg/min from -180 to 0 minutes. At that time glucose was infused intravenously to mimic the systemic appearance of 50g of oral glucose. Exendin-9,39 infusion raised fasting glucose (Panel A), but did not alter insulin (Panel B) or C-peptide (Panel C) concentrations. Exendin-9,39 infusion raised fasting glucagon concentrations and impaired post-challenge suppression by glucose. Values plotted are Means ± SEMs. *$P < 0.05$ for a paired t-test. Note the glucagon assay used in this experiment was a Radio-Immunoassay (Linco Research, St. Louis, MO).

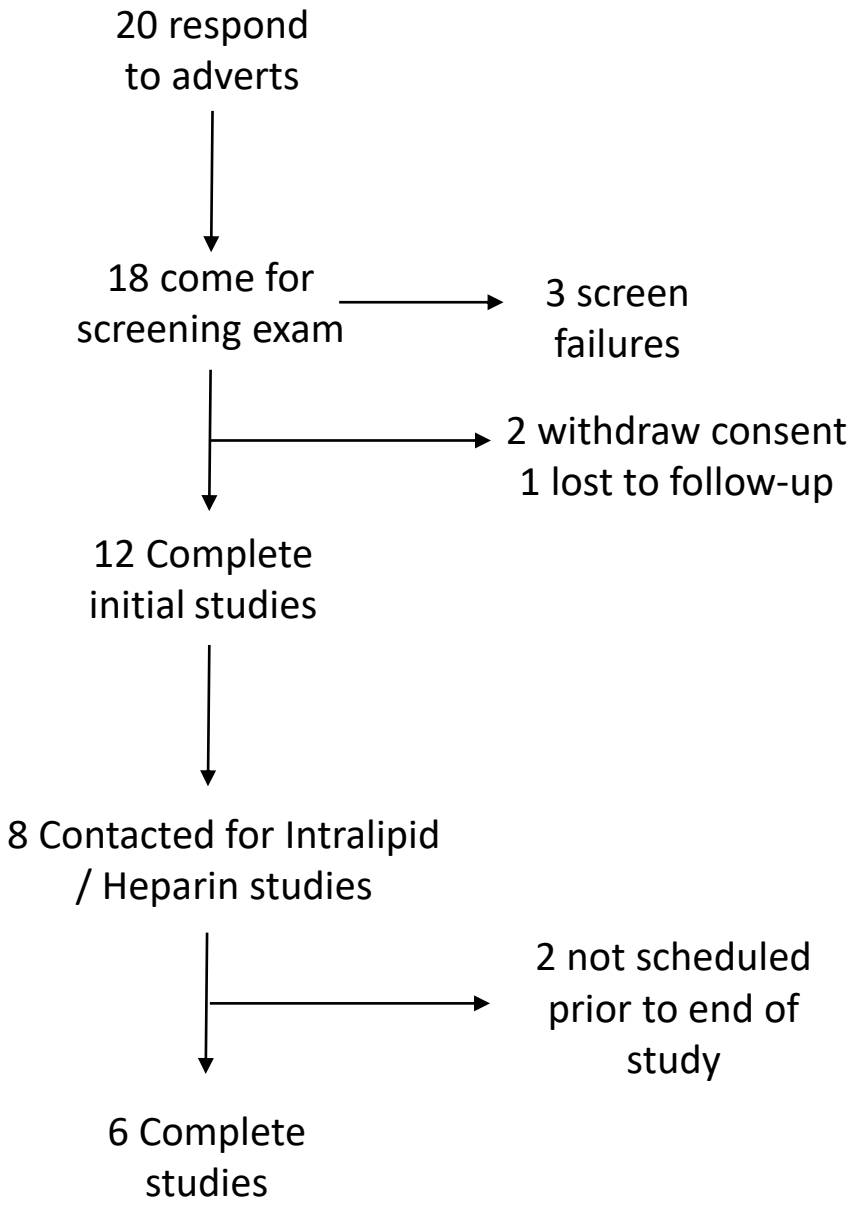


Supplementary Figure 2: Glucose insulin, C-peptide and glucagon concentrations in a subset of subjects without diabetes studied on two occasions where free fatty acids were increased are shown in Panels A, C, E and G respectively. (○) represent concentrations observed during saline infusion and (●). Values plotted are Means ± SEMs. The corresponding symmetrical percent change in fasting and clamp concentrations attributable to exendin 9-39 in the absence (◇) and in the presence (◆) of FFA elevation are shown in Panels B, D, F and H respectively.

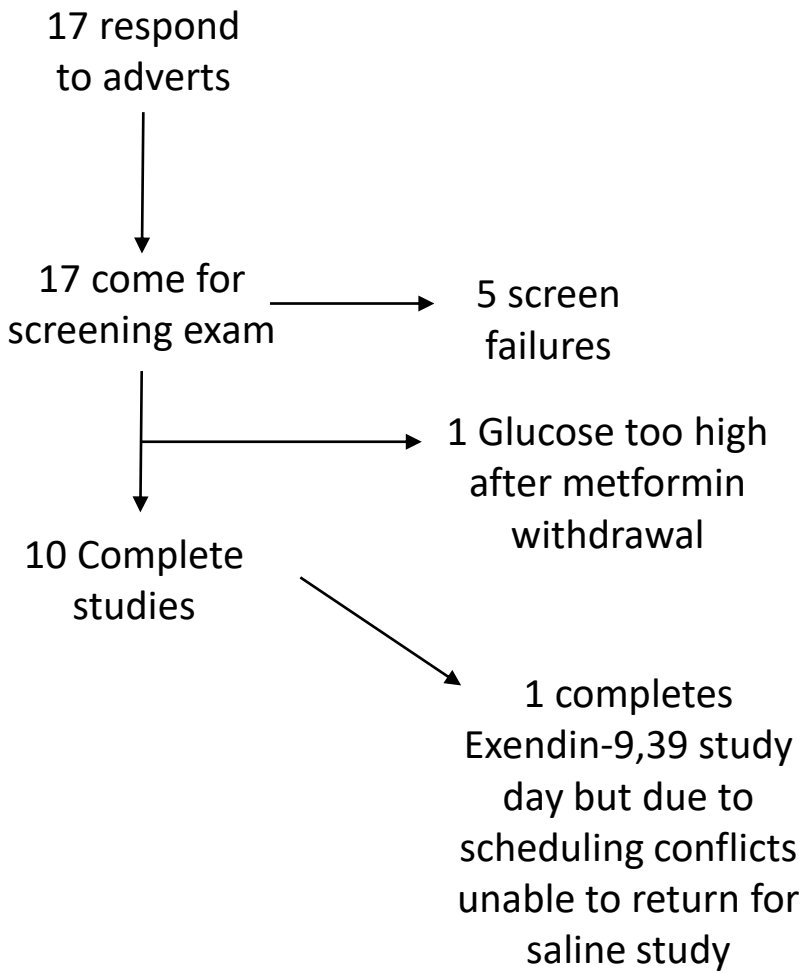


Supplementary Figure 3: Glucose insulin and C-peptide concentrations after administration of 1mg glucagon in the presence (■) and absence (□) of exendin 9-39 in subjects with type 2 diabetes (Panels A, D and G respectively). Values plotted are Means ± SEMs. The change in area under the curve (AUC) of glucose, insulin and C-peptide (□, ■; ○, ●; ◇, ◆ - subjects with type 2 diabetes [T2DM], without diabetes [non-DM] and the subset studied with free fatty acid elevation [non-DM+FFA]) in response to glucagon are shown in Panels B, E and H respectively. The symmetrical % change in AUC for glucose, insulin and C-peptide attributable to exendin 9-39 are shown in Panels C, F and I respectively. *P < 0.05 using a paired t-test.

Subjects without Diabetes



Subjects with Type 2 Diabetes



TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	✓	2
		• Structured abstract recommended	✓	2
		• Information on target population or study sample	✓	2
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	4-5
		• Theories used in designing behavioral interventions	NA	NA
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	14
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	14
		• Recruitment setting	✓	14
		• Settings and locations where the data were collected	✓	14-16
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	✓	15
		○ Content: what was given?	✓	15
		○ Delivery method: how was the content given?	✓	15
		○ Unit of delivery: how were the subjects grouped during delivery?	✓	15
		○ Deliverer: who delivered the intervention?	✓	15
		○ Setting: where was the intervention delivered?	✓	15
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	15
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	✓	15
		○ Activities to increase compliance or adherence (e.g., incentives)	NA	NA
Objectives	5	• Specific objectives and hypotheses	✓	5
Outcomes	6	• Clearly defined primary and secondary outcome measures	✓	5
		• Methods used to collect data and any methods used to enhance the quality of measurements	✓	16
		• Information on validated instruments such as psychometric and biometric properties	NA	NA
Sample Size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	✓	17
Assignment Method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	✓	14-15
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	✓	14-15
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	✓	14-15

TREND Statement Checklist

Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	NA	NA
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	✓	15-17
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	✓	15-17
Statistical Methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	✓	16-17
		• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	✓	16-17
		• Methods for imputing missing data, if used	NA	NA
		• Statistical software or programs used	✓	16-17
Results				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	✓	↑ Supplement
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	✓	
		○ Assignment: the numbers of participants assigned to a study condition	✓	
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	✓	
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	✓	Diagram
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	↓
		• Description of protocol deviations from study as planned, along with reasons	NA	NA
Recruitment	13	• Dates defining the periods of recruitment and follow-up	NA	NA
Baseline Data	14	• Baseline demographic and clinical characteristics of participants in each study condition	✓	28
		• Baseline characteristics for each study condition relevant to specific disease prevention research	NA	NA
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	NA	NA
		• Comparison between study population at baseline and target population of interest	✓	28
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	28

TREND Statement Checklist

Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	Figures
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	NA	NA
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	✓	Results Part 5-7
		• Inclusion of null and negative findings	✓	
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	✓	
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✓	Results Part 5-7
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	NA	NA
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	9-14
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	9-14
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✓	9-14
		• Discussion of research, programmatic, or policy implications	✓	9-14
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	NA	NA
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory	✓	9-14

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/

ICMJE DISCLOSURE FORM

Date: 8/23/2023

Your Name: Andrew A. Welch

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

Manuscript Number (if known): **173495-JCI-RG-1**

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Date: 8/23/2023

Your Name: Rahele A. Farahani

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

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Your Name: Aoife M. Egan

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Your Name: Marcello C. Laurenti

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

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Your Name: Max Vella

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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 8/23/2023

Your Name: Kent R. Bailey

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

Manuscript Number (if known): **173495-JCI-RG-1**

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

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4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

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ICMJE DISCLOSURE FORM

Date: 8/23/2023

Your Name: Claudio Cobelli

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

Manuscript Number (if known): **173495-JCI-RG-1**

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ICMJE DISCLOSURE FORM

Date: 8/23/2023

Your Name: Chiara Dalla Man

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

Manuscript Number (if known): **173495-JCI-RG-1**

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ICMJE DISCLOSURE FORM

Date: 8/23/2023

Your Name: Adrian Vella

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

Manuscript Number (if known): **173495-JCI-RG-1**

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		NIH NIDDK DK78646	
		NIH NIDDK DK116231	
		NIH NIDDK DK126206	Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		Novo Nordisk	Investigator-initiated grant
3	Royalties or licenses	☒ **None**	

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4	Consulting fees	☒ **None**	
		Rezolute	Hypoglycemic disorders
		Crinetics	Hypoglycemic disorders
		Zeeland	Hypoglycemic disorders
		vTv Therapeutics	Glucokinase activator for Rx of T2DM
		Hanmi Pharamceuticals	Hypoglycemic disorders
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
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ICMJE DISCLOSURE FORM

Date: 8/23/2023

Your Name: Aleksey Matveyenko

Manuscript Title: **Glucagon-Like Peptide-1 Receptor blockade impairs islet secretion and glucose metabolism in humans**

Manuscript Number (if known): **173495-JCI-RG-1**

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