



Effects of a 6-week subcutaneous infusion of native GIP alone or as add-on to semaglutide in people with type 2 diabetes: a single-centre, double-blind, parallel-group, randomised, placebo-controlled trial

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Summary

Background The long-term glycaemic effects of glucose-dependent insulinotropic polypeptide (GIP) remain unclear. We aimed to assess whether a 6-week subcutaneous infusion of GIP alone and in combination with the GLP-1 receptor agonist semaglutide would enhance glycaemic control in individuals with type 2 diabetes.

Methods This single-centre, double-blind, parallel-group, randomised, placebo-controlled trial was conducted at the Center for Clinical Metabolic Research (Hellerup, Denmark). Inclusion criteria were age 18–74 years; a diagnosis of type 2 diabetes for at least 6 months; stable treatment; HbA_{1c} of 6.5–10.5% (48–91 mmol/mol); and a BMI of 25–50 kg/m². Participants were randomly assigned (1:1:1:1), using a block randomisation list, to receive either placebo plus placebo, placebo plus GIP, semaglutide plus placebo, or semaglutide plus GIP (all self-administered subcutaneously). The regimen was 8-week semaglutide or placebo run-in period (4 weeks at 0.25 mg then 4 weeks at 0.50 mg once per week), after which participants continued 0.50 mg semaglutide or placebo for an additional 6 weeks while receiving continuous subcutaneous infusions of GIP or placebo (16 pmol/kg per min). Participants and investigators were masked to treatment assignment. The primary outcome was change in 14-day mean glucose concentration assessed by continuous glucose monitoring from baseline to the end of treatment at 14 weeks, assessed in the efficacy population. This study is registered at ClinicalTrials.gov, NCT05078255 (completed).

Findings Between Jan 31, 2022, and Sept 4, 2024, we assessed 134 individuals with type 2 diabetes for eligibility, of whom 73 were ineligible. We enrolled and randomly assigned 61 participants (15 to placebo plus placebo, 16 to placebo plus GIP, 15 to semaglutide plus placebo, and 15 to semaglutide plus GIP). Ten (16%) participants discontinued the study. Participants had a median age of 64.0 years (IQR 60.0–68.0), HbA_{1c} of 54.0 mmol/mol (49.0–60.0), diabetes duration of 6.3 years (4.2–9.8), and a mean BMI of 31.6 kg/m² (SD 4.8). 22 (36%) participants were female and 39 (64%) were male and all self-reported as White. Fasting concentrations of intact (bioactive) GIP at the end of treatment on week 14 were mean 7 pmol/L (SD 4) in the placebo plus placebo group, 45 pmol/L (43) in the placebo plus GIP group, 10 pmol/L (6) in the semaglutide plus placebo group, and 85 pmol/L (92) in the semaglutide plus GIP group; whereas fasting concentrations of total GIP were 14 pmol/L (7), 375 pmol/L (377), 18 pmol/L (19), and 527 pmol/L (338), respectively. The estimated effect of GIP on change in 14-day mean sensor-detected glucose from baseline to end of treatment was 0.80 mmol/L (97.5% CI –0.18 to 1.80; $p=0.13$ in the placebo plus GIP vs placebo plus placebo groups) and 0.05 mmol/L (–0.85 to 0.95; $p=1.00$ in the semaglutide plus GIP vs semaglutide plus placebo groups). Injection site reactions were the most common adverse event (22 [36%]). Gastrointestinal adverse events were more frequent with semaglutide (nine [60%] with placebo plus placebo, 11 [69%] with placebo plus GIP, 11 [73%] with semaglutide plus placebo, and 12 [80%] with semaglutide plus GIP).

Interpretation 6 weeks of subcutaneous GIP infusion as add-on to placebo or semaglutide did not improve glycaemic control in individuals with type 2 diabetes at the prespecified target of 1.50 mmol/L. Due to dropouts, we cannot draw firm conclusions on the effects of GIP as add-on to placebo.

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Introduction

Type 2 diabetes is a chronic metabolic condition with increasing prevalence that affects an estimated 462 million individuals worldwide.¹ This condition is

characterised by insulin resistance and impaired insulin secretion, and is associated with metabolic syndrome (abdominal obesity, high blood pressure, impaired fasting glucose, insulin resistance, and dyslipidaemia).²

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Research in context

Evidence before this study

The long-term effects of exogenous glucose-dependent insulinotropic polypeptide (GIP) in humans remain unclear. After the introduction of agents with agonistic or antagonistic properties at the GIP receptor for individuals with type 2 diabetes and obesity, there is a need for a broader understanding of long-term supraphysiological GIP receptor activation. We considered evidence on the physiological actions of GIP and its relevance to metabolic regulation in type 2 diabetes. Our 2023 narrative review show that the insulinotropic effect of GIP is markedly reduced or absent in participants with type 2 diabetes, although its glucagonotropic effect is preserved, which contributes to higher postprandial glucose concentrations in some cases. Exogenous GIP has not shown appetite or weight lowering effects in humans, and short-term coadministration of GIP and glucagon-like peptide 1 (GLP-1) does not enhance glucose lowering beyond GLP-1 alone in individuals with type 2 diabetes. Physiological and interventional evidence indicates that the metabolic role of GIP in humans is incompletely defined and there are no long-term studies of supraphysiological GIP exposure in humans. To examine the safety profile of exogenous GIP, we published a systematic review in 2024. For this review, we searched PubMed using the Medical Subject Headings term “gastric inhibitory polypeptide” and other search terms: “gastric inhibitory polypeptide”, “glucose-dependent insulinotropic polypeptide”, “glucose dependent insulinotropic polypeptide”, and “GIP”. We included trials administering synthetic human GIP and excluded those using porcine GIP or no GIP. 52 (78%) of

67 studies did not report safety events and others described mild and transient effects, such as small increases in heart rate, blood pressure changes, occasional gastrointestinal symptoms, and transient hypoglycaemia in a participant with end-stage renal disease. No hypersensitivity reactions were reported. The review concluded that short-term GIP administration is generally well tolerated, but long-term safety of continuous GIP exposure in humans is unknown.

Added value of this study

This study offers insight into the glucometabolic effects of 6-week native GIP alone and combined with the GLP-1 receptor agonist semaglutide in individuals with type 2 diabetes. For all glycaemic endpoints (mean glucose, glycaemic variability, times in ranges, fasting plasma glucose, HbA1c, plasma glucose excursions after oral glucose ingestion, and bodyweight), there were no statistically significant treatment effects of native GIP.

Implications of all the available evidence

Incretin-based therapies have considerably improved the treatment options for individuals with type 2 diabetes and obesity, for whom dual GIP and GLP-1 receptor agonists have substantial glucose-lowering and weight-reducing properties; however, native GIP administered in our study at supraphysiological doses for 6 weeks was not associated with improvements in glycaemic control and bodyweight in participants with type 2 diabetes. Future studies should further explore the differential effects of isolated long-term GIP receptor activation versus dual GIP and GLP-1 receptor agonism.

A key component of the pathophysiology of type 2 diabetes is a diminished insulinotropic effect of the two incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).³ These hormones are secreted from enteroendocrine L-cells and K-cells in the small intestine in response to nutrient intake, and enhance postprandial insulin secretion from β -cells, which is known as the incretin effect.⁴ Incretin hormone receptors are also widely expressed in other tissues, in which they mediate various physiological effects.⁵ GLP-1 reduces glucagon concentrations, suppresses appetite, slows gastric emptying, and increases heart rate, whereas GIP might increase glucagon secretion during normal-to-low blood glucose concentrations, raises heart rate, lowers blood pressure, and decreases bone resorption.⁵

There has been a greater interest in GLP-1 than GIP as a therapeutic option due to its more preserved insulinotropic capacity and appetite-regulating properties when administered to individuals with type 2 diabetes and obesity.⁶ GIP and particularly GLP-1 are rapidly degraded by the enzyme DPP-4, resulting in short half-lives of a few minutes.^{7,8} To overcome this issue, DPP-4-resistant GLP-1 analogues have been developed

and introduced for individuals with type 2 diabetes and obesity.⁶ Further development has led to longer-acting, once per week formulations (eg, semaglutide) with improved glycaemic regulation and substantial bodyweight lowering effects.⁹

Despite the markedly reduced insulinotropic effect of GIP in individuals with type 2 diabetes, the role of GIP in the pharmacological treatment of type 2 diabetes and obesity has regained attention.^{6,10} This renewed interest is partly due to evidence that the insulinotropic effect of GIP can be partly restored when blood glucose is normalised, along with promising results from dual agonists that target both GIP and GLP-1 receptors.^{11,12} In particular, tirzepatide (a unimolecular dual GIP and GLP-1 receptor agonist) substantially improves glycaemic control and weight management in individuals with type 2 diabetes;¹³ however, the specific long-term effects of supraphysiological GIP receptor activation alone and in combination with GLP-1 receptor activation remain unclear.^{6,14}

We aim to assess whether a 6-week subcutaneous infusion of GIP alone and in combination with the GLP-1 receptor agonist semaglutide would enhance glycaemic control in individuals with type 2 diabetes. We also

elucidate the metabolic effects of sustained treatment on bodyweight, blood pressure, and insulin sensitivity.

Methods

Study design and participants

This single-centre, double-blind, parallel-group, randomised, placebo-controlled trial was conducted at the Center for Clinical Metabolic Research (Gentofte Hospital, University of Copenhagen, Hellerup, Denmark). Inclusion criteria were age 18–74 years; a diagnosis of type 2 diabetes for at least 6 months; stable treatment with diet and exercise or any treatment combination (metformin, SGLT2 inhibitors, DPP-4 inhibitors, and sulfonylureas), or both, with 14-day washout before study procedures; HbA_{1c} of 6·5–10·5% (48–91 mmol/mol); and a BMI of 25–50 kg/m². Exclusion criteria were type 1 diabetes; hypersensitivity to the trial treatment; pregnancy or breastfeeding; recent acute decompensation of glycaemic control; previous or concurrent participation in clinical trials; use of medications or conditions that could interfere with study outcomes; clinically significant endocrine, psychiatric, cardiovascular, or malignant disease; substance misuse; abnormal laboratory safety parameters; and factors that could compromise participant safety, compliance, or data integrity. The complete list of exclusion criteria is provided in the published study protocol.¹⁵ Sex was self-reported. All participants provided oral and written consent. This study was approved by the Danish Medicines Agency (EudraCT 2020–004774–22) and the Scientific Ethics Committees for the Capital Region of Denmark (H-20070184). The study was monitored by the Good Clinical Practice Unit (Copenhagen University Hospital, Frederiksberg Hospital, Copenhagen, Denmark). In a protocol amendment on Oct 31, 2022, we broadened the eligibility (medication history with washout, wider HbA_{1c} changed from 7·0–10·5% [53–91 mmol/mol] to 6·5–10·5% [48–91 mmol/mol] and BMI eligibility criteria were changed from ≥27 to ≤50 kg/m² and from ≥25 to ≤50 kg/m²) after eight enrolments. Study participants were recruited at clinics, patient organisations, and on social media. We engaged two individuals with type 2 diabetes to identify ways to reduce possible participant burden and improve study related communication and participant-facing materials. Participant feedback informed visit overviews and device illustrations. This study is registered at ClinicalTrials.gov, NCT05078255 (completed).

Randomisation and masking

Participants were randomly assigned (1:1:1:1) to receive either placebo plus placebo, placebo plus GIP, semaglutide plus placebo, or semaglutide plus GIP (appendix p 19). Each type of study medication (pens with semaglutide or placebo and vials with GIP or placebo) had identical appearance. Participants and investigators were masked to treatment assignment. An unmasked staff member created a computer generated a block randomisation

list (Sealed Envelope, London, UK), allocated study medication, and had sole access to the allocation files. In a medical emergency, concealed envelopes with treatment assignment were available for investigators and oversight was performed by an unmasked staff member from the Good Clinical Practice Unit.

Procedures

Semaglutide or saline placebo dispensing pens were produced and delivered by Novo Nordisk (Copenhagen, Denmark). Unmasked staff labelled and dispensed the pens with semaglutide or placebo, and participants self-administered the medication subcutaneously once per week. Vials with good manufacturing practice grade GIP or saline placebo were labelled and dispensed by unmasked staff and prepared by the hospital pharmacy. Formulation and stability details for GIP and semaglutide are provided in the appendix (p 23).

Participants self-administered GIP or placebo using a commercially available insulin pump (Minimed 640G, Medtronic, Dublin, Ireland). The treatment regimen consisted of an 8-week semaglutide or placebo run-in period (4 weeks at 0·25 mg then 4 weeks at 0·50 mg once per week), after which participants continued 0·50 mg semaglutide or placebo for an additional 6 weeks while receiving continuous subcutaneous infusions of GIP or placebo (16 pmol/kg per min). GIP or placebo was initiated after the semaglutide titration period to ensure participants were at a therapeutic semaglutide dose and steady state and reduce the duration of pump treatment to a feasible timeframe. The 0·50 mg dose of semaglutide was chosen to minimise gastrointestinal adverse events that might confound tolerability assessments related to GIP. Participants maintained a diary documenting treatment administration, side-effects, illnesses, and changes in concomitant medications.

Continuous glucose monitoring (CGM; FreeStyle Libre Pro iQ, Abbott Diabetes Care, Alameda, CA, USA) was conducted for 14 days at baseline (before starting semaglutide or placebo), before the GIP or placebo add-on (at 6–8 weeks), and during the final treatment phase (at 12–14 weeks; appendix p 20). Participants and investigators were masked to these data and an unmasked staff member handled data collection. None of the participants had their own CGM devices. Oral glucose tolerance tests (OGTT; 75 g of glucose in 300 mL of water) were conducted at the same three timepoints. Semaglutide or placebo was initiated in the afternoon after the first OGTT and GIP or placebo was initiated after the second test. To estimate insulin sensitivity and β -cell responsiveness, we assessed plasma concentrations of glucose, insulin, and C-peptide from the OGTT samples (fasting and post-load up to 120 min).

OGTT samples were processed as per the protocol (preanalytical details shown in the appendix p 24). Plasma glucose concentrations, HbA_{1c}, insulin, C-peptide, triglycerides, cholesterol, C-reactive protein, and

See Online for appendix

paracetamol were measured using standardised methods. GIP (intact and total) and total GLP-1 were analysed in plasma samples using an in-house radioimmunoassay, as previously described.^{8,16} Plasma glucagon was analysed with an ELISA (10–1271–01; Mercodia, Uppsala, Sweden).

We assessed safety parameters including participant-reported side-effects, physical examinations, blood pressure, heart rate, and organ-specific blood tests (eg, liver and kidney function) on OGTT visits and three additional safety visits (at weeks 1, 9, and 11). Treatment ended after the third OGTT and participants attended a follow-up visit after 4 weeks.

Outcomes

The primary outcome was change in 14-day mean glucose concentration assessed by CGM from baseline to the end of treatment at 14 weeks, assessed in the efficacy population (defined as all randomly assigned participants).

The secondary outcomes were change in 14-day glycaemic variability determined by CGM and time in glycaemic ranges as defined in the International Consensus Statement¹⁷ from baseline to the end of treatment; glycaemic control assessed by HbA_{1c}; bodyweight; waist circumference; blood pressure and heart rate. The outcomes of liver status, lipid profile, inflammatory markers, blood microbiota composition, and brown adipose tissue will be published elsewhere. As post-hoc outcomes, we included fasting plasma concentrations of GIP, GLP-1, and glucagon. Secondary outcomes from OGTT were glycaemic status (fasting plasma concentrations and area under the curve [AUC] of

glucose, insulin, and C-peptide); insulin sensitivity; β -cell responsiveness to glucose assessed by calculation of the insulinogenic index; and plasma concentrations of intact and total GIP, total GLP-1, glucagon, and gastric emptying (assessed by the paracetamol absorption test). The outcomes of bile acid metabolism and bone homeostasis will be published elsewhere. All secondary outcomes were assessed in the efficacy population. Safety outcomes were the number and frequency of treatment-emergent adverse events.

Statistical analysis

Sample size was estimated using the power *t* test function in R (version 4.0.3). We chose a minimal relative difference for the two coprimary comparisons (placebo plus placebo vs placebo plus GIP and semaglutide plus placebo vs semaglutide plus GIP) of 1.50 mmol/L, which is similar to the HbA_{1c} change assumption from −0.74% to −1.44% corresponding to a clinically meaningful change of 1–2 mmol/L in estimated plasma glucose. This minimal relative difference also corresponds to the end of treatment difference in HbA_{1c} reported between dulaglutide and intermediate dose tirzepatide groups.¹⁸ Based on unpublished GLYCOHEMO trial data (NCT03909269) of sensor-detected 7-day mean glucose from 40 participants with type 2 diabetes (Bomholt T, University Copenhagen Hospital, Rigshospitalet, Copenhagen, Denmark; personal communication), we anticipated that the SD at baseline and follow-up would be approximately 1.9 mmol/L and the correlation coefficient between baseline and follow-up would be at

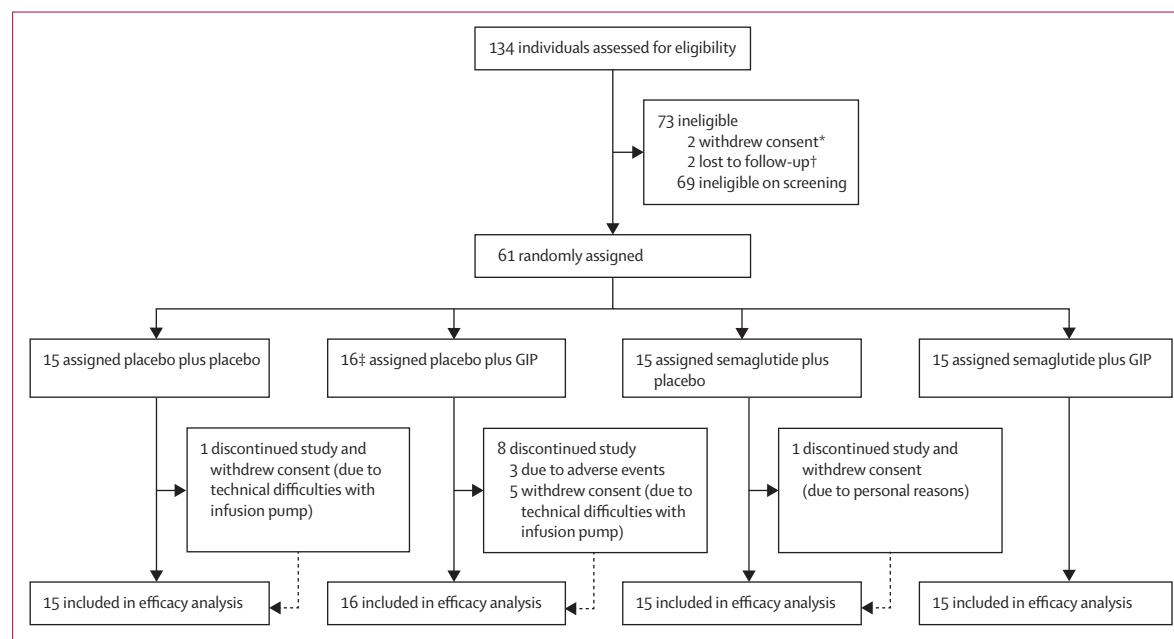


Figure 1: Trial profile

61 participants were included in the efficacy analysis (mixed model). GIP=glucose-dependent insulinotropic polypeptide. *Ineligible on screening due to not meeting inclusion criteria. †Lost to follow-up due to no response to contact despite repeated attempts. ‡The short trial timeframe allowed replacement of only one withdrawn participant.

least 0·70; thus, the SD of change from baseline to follow-up should be at most 1·09 mmol/L implying that 13 participants would be needed in each treatment group to detect the minimal relative difference with a power of 0·85 at a Bonferroni-adjusted significance level of 0·025 (α split by two). To ensure power despite an assumed dropout rate of 5–10%, we planned to include 60 participants with a maximum of eight replacements

for those withdrawn. A DELTA² sample size reporting checklist is provided in the appendix (p 23).

Glycaemic variability was assessed as coefficient of variance ($100 \times \text{SD}/\text{mean glucose}$) and insulin sensitivity was assessed by homoeostasis model analysis of insulin resistance and Matsuda index. All analyses (except post-hoc safety analyses) were carried out according to a previously published statistical analysis plan.¹⁵ The

	Placebo plus placebo (n=15)	Placebo plus GIP (n=16)	Semaglutide plus placebo (n=15)	Semaglutide plus GIP (n=15)	Total (n=61)
Age, years	66·0 (59·5–69·0)	64·0 (60·8–67·0)	64·0 (62·0–68·5)	62·0 (57·5–68·5)	64·0 (60·0–68·0)
Sex					
Female	5 (33%)	7 (44%)	6 (40%)	4 (27%)	22 (36%)
Male	10 (67%)	9 (56%)	9 (60%)	11 (73%)	39 (64%)
HbA _{1c} , mmol/mol	55·0 (49·0–62·5)	53·0 (49·0–58·5)	54·0 (51·0–57·0)	54·0 (49·5–59·0)	54·0 (49·0–60·0)
HbA _{1c} , %	7·2% (6·6–7·9)	7·0% (6·6–7·5)	7·1% (6·8–7·4)	7·1% (6·7–7·5)	7·1% (6·6–7·6)
Fasting plasma glucose, mmol/L	8·1 (7·8–9·7)	8·5 (7·6–8·3)	8·2 (7·4–9·8)	8·6 (8·2–9·6)	8·3 (7·8–9·6)
Duration of diabetes, years	7·4 (5·1–14·0)	5·7 (4·6–9·5)	5·0 (3·4–9·3)	6·2 (5·0–8·3)	6·3 (4·2–9·8)
Mean BMI, kg/m ²	31·9 (4·3)	32·8 (5·1)	29·9 (4·2)	31·7 (5·3)	31·6 (4·8)
Mean bodyweight, kg	96·5 (15·1)	98·1 (15·6)	87·6 (10·9)	93·5 (16·3)	94·0 (14·8)
Mean waist circumference, cm	111·0 (9·4)	111·2 (13·4)	104·2 (10·0)	107·4 (11·0)	108·5 (11·2)
C-peptide, pmol/L	905·2 (279·6)	1045·8 (404·0)	946·5 (391·0)	876·3 (268·7)	945·8 (341·3)
Mean glucose, mmol/L (at 14 days)*	9·1 (2·4)	8·4 (1·7)	8·3 (1·2)	8·8 (1·3)	8·7 (1·7)
Blood pressure					
Systolic, mm Hg	138·1 (11·7)	138·1 (14·5)	127·2 (11·1)	136·3 (13·9)	134·9 (13·4)
Diastolic, mm Hg	79·1 (5·7)	78·5 (6·8)	79·4 (8·3)	81·5 (6·5)	79·6 (6·8)
Pulse rate, beats per minute	66·1 (6·7)	67·7 (10·7)	72·0 (9·1)	73·0 (8·4)	69·7 (9·1)
Diabetes medication					
Metformin	8 (53%)	10 (63%)	7 (47%)	9 (60%)	34 (56%)
Metformin and SGLT2 inhibitor	5 (33%)	2 (13%)	6 (40%)	3 (20%)	16 (26%)
Metformin and DPP-4 inhibitor	2 (13%)	0	1 (7%)	0	3 (5%)
Metformin and sulfonylurea	0	1 (6%)	0	0	1 (2%)
SGLT2 inhibitor	0	0	1 (7%)	1 (7%)	2 (3%)
Metformin and SGLT2 and DPP-4 inhibitors	0	0	0	1 (7%)	1 (2%)
No diabetes medication	0	3 (19%)	0	1 (7%)	4 (7%)
Comorbidities					
Gastrointestinal	3 (20%)	3 (19%)	6 (40%)	1 (7%)	13 (21%)
Orthopaedic	2 (13%)	1 (6%)	1 (7%)	4 (27%)	8 (13%)
Neurological	1 (7%)	1 (6%)	0	1 (7%)	3 (5%)
Endocrine (other than type 2 diabetes)	1 (7%)	1 (6%)	0	0	2 (3%)
Lung	7 (47%)	4 (25%)	7 (47%)	4 (27%)	22 (36%)
Concomitant medication					
Statin	9 (60%)	11 (69%)	12 (80%)	8 (53%)	40 (66%)
Renin-angiotensin system blockers	8 (53%)	5 (31%)	9 (60%)	8 (53%)	30 (31%)
Antithrombotic	5 (33%)	3 (19%)	6 (40%)	5 (33%)	19 (31%)
Opioid	0	1 (6%)	0	1 (7%)	2 (3%)
Non-steroid anti-inflammatory drugs	3 (20%)	0	0	2 (13%)	5 (8%)
Diabetes complications					
Neuropathy	4 (27%)	3 (19%)	1 (7%)	3 (20%)	11 (18%)
Retinopathy	0	0	1 (7%)	1 (7%)	2 (3%)

Data are median (IQR), n (%), or mean (SD). All participants self-reported as White European (recruited in Denmark). Additional information defining the comorbidity, concomitant medication, and diabetes complications is shown in the appendix (p 25). GIP=glucose-dependent insulinotropic polypeptide. *Measured by continuous glucose monitoring.

Table 1: Baseline clinical characteristics (efficacy population)

	Placebo plus placebo	Placebo plus GIP	Estimated treatment difference (97.5% CI); p value	Semaglutide plus placebo	Semaglutide plus GIP	Estimated treatment difference (97.5% CI); p value
Change in 14-day mean glucose, mmol/L (primary endpoint)	..	..	0.80 (-0.18 to 1.80); p=0.13	..	..	0.05 (-0.85 to 0.95); p=1.00
Week 0	9.1 (2.4)	8.4 (1.7)	..	8.3 (1.2)	8.8 (1.3)	..
Week 14	8.4 (1.6)	8.9 (1.6)	..	6.5 (0.5)	6.8 (1.4)	..
Change from baseline	-0.5 (2.0)	0.2 (1.5)	..	-1.7 (1.0)	-2.0 (1.0)	..
Glycaemic variability, coefficient of variation %	..	..	-0.62 (-3.83 to 2.60); p=0.93	..	..	1.44 (-1.33 to 4.22); p=0.59
Week 0	22.2 (4.4%)	22.1 (2.9%)	..	20.7 (2.3%)	22.0 (2.9%)	..
Week 14	22.0 (3.9%)	21.0 (2.7%)	..	18.2 (2.4%)	20.2 (5.4%)	..
Change from baseline	-0.4 (3.2%)	-1.2 (4.5%)	..	-2.6 (2.0%)	-1.9 (6.1%)	..
Time above range (>13.9), mmol/L	..	..	1.27 (-0.62 to 3.17); p=0.49	..	..	0.20 (-1.44 to 1.83); p=0.95
Week 0	7.5 (16.7%)	3.9 (7.9%)	..	1.0 (1.2%)	3.0 (3.9%)	..
Week 14	3.0 (4.6%)	4.1 (4.3%)	..	0	0.7 (2.1%)	..
Change from baseline	-4.2 (14.0%)	-2.4 (6.7%)	..	-0.9 (1.2%)	-2.3 (4.5%)	..
Time above range (10.1-13.9), mmol/L	..	..	6.87 (-2.55 to 16.30); p=0.49	..	..	4.24 (-4.50 to 13.00); p=0.61
Week 0	23.5 (17.1%)	18.2 (16.1%)	..	18.1 (15.2%)	23.8 (15.7%)	..
Week 14	20.2 (15.9%)	24.2 (18.4%)	..	1.5 (1.1%)	7.5 (13.0%)	..
Change from baseline	-1.3 (19.5%)	3.9 (13.5%)	..	-15.3 (14.8%)	-16.3 (13.7%)	..
Time in range (3.9-10.0), mmol/L	..	..	-8.30 (-19.21 to 2.60); p=0.49	..	..	-4.42 (-14.36 to 5.52); p=0.66
Week 0	27.8 (12.0%)	28.0 (12.3%)	..	32.6 (10.2%)	33.5 (7.1%)	..
Week 14	29.9 (12.6%)	35.3 (12.9%)	..	13.5 (7.7%)	16.3 (15.3%)	..
Change from baseline	2.5 (14.3%)	11.8 (14.8%)	..	-18.3 (11.2%)	-17.2 (13.9%)	..
Time in tight range (3.9-7.8), mmol/L	..	..	-15.65 (-32.64 to 1.33); p=0.39	..	..	-5.76 (-21.58 to 10.10); p=0.74
Week 0	41.2 (29.8%)	49.5 (27.0%)	..	48.3 (25.0%)	39.5 (22.7%)	..
Week 14	46.7 (29.5%)	36.3 (29.7%)	..	84.6 (8.4%)	74.7 (28.2%)	..
Change from baseline	2.9 (29.8%)	-12.6 (28.8%)	..	34.1 (23.9%)	35.2 (19.9%)	..
Time below range (3.0-3.8), mmol/L	..	..	-0.16 (-0.83 to 0.51); p=0.87	..	..	0.41 (-0.15 to 0.96); p=0.49
Week 0	0.06 (0.16%)	0.37 (1.26%)	..	0.04 (0.15%)	0.25 (0.61%)	..
Week 14	0.10 (0.26%)	0.02 (0.07%)	..	0.40 (0.64%)	0.85 (1.23%)	..
Change from baseline	0.03 (0.26%)	-0.62 (1.58%)	..	0.36 (0.56%)	0.59 (1.18%)	..
Time below range (<3.0), mmol/L	..	..	-0.04 (-0.15 to 0.08); p=0.78	..	..	-0.02 (-0.12 to 0.07); p=0.87
Week 0	0.01 (0.02%)	0.04 (0.10%)	..	0.01 (0.02%)	0.04 (0.07%)	..
Week 14	0.07 (0.18%)	0.04 (0.11%)	..	0.04 (0.12%)	0.02 (0.08%)	..
Change from baseline	0.06 (0.18%)	-0.01 (0.18%)	..	0.03 (0.10%)	-0.02 (0.09%)	..
HbA _{1c} , mmol/mol	..	..	1.87 (-1.96 to 5.71); p=0.61	..	..	-0.02 (-3.68 to 3.64); p=0.99
Week 0	56.5 (8.8)	55.5 (9.2)	..	55.9 (7.8)	55.4 (6.8)	..
Week 14	53.2 (9.3)	56.4 (10.0)	..	43.6 (6.6)	43.6 (3.3)	..
Change from baseline	-2.5 (7.1)	-2.1 (5.4)	..	-11.0 (5.5)	-12.0 (5.5)	..
Fasting concentration of plasma glucose, mmol/L	..	..	0.04 (-0.93 to 1.00); p=0.97	..	..	-0.42 (-1.30 to 0.45); p=0.61
Week 0	9.3 (2.6)	8.6 (1.7)	..	8.7 (1.8)	8.9 (1.0)	..
Week 14	8.7 (1.5)	8.4 (1.3)	..	7.2 (1.1)	6.8 (1.2)	..
Change from baseline	-0.5 (2.1)	-0.8 (1.6)	..	-1.6 (2.0)	-2.1 (1.0)	..
Bodyweight, kg	..	..	0.28 (-1.80 to 2.30); p=0.95	..	..	-0.08 (-2.01 to 1.86); p=0.97
Week 0	96.5 (15.1)	98.1 (15.6)	..	87.6 (10.9)	93.5 (16.3)	..
Week 14	96.2 (15.8)	99.9 (15.9)	..	82.6 (10.6)	89.7 (17.9)	..
Change from baseline	-1.0 (2.4)	-0.78 (2.0)	..	-4.3 (2.4)	-4.1 (3.2)	..
Waist circumference, cm	..	..	2.65 (-1.24 to 6.53); p=0.49	..	..	0.30 (-3.30 to 4.00); p=0.95
Week 0	111.0 (9.4)	111.2 (13.4)	..	104.2 (10.0)	107.4 (11.0)	..
Week 14	107.9 (10.2)	109.6 (16.8)	..	99.3 (11.2)	104.7 (15.4)	..
Change from baseline	-3.2 (4.2)	-0.5 (5.0)	..	-4.0 (4.5)	-2.6 (5.6)	..

(Table 2 continues on next page)

	Placebo plus placebo	Placebo plus GIP	Estimated treatment difference (97.5% CI); p value	Semaglutide plus placebo	Semaglutide plus GIP	Estimated treatment difference (97.5% CI); p value
(Continued from previous page)						
Fasting concentration of plasma glucagon, pmol/L	..	..	1.62 (-1.51 to 4.74); p=0.59	..	..	0.93 (-1.76 to 3.62); p=0.76
Week 0	12.2 (6.2)	13.1 (4.6)	..	13.1 (5.5)	11.1 (4.7)	..
Week 14	11.2 (5.5)	13.0 (6.5)	..	11.3 (5.2)	10.3 (5.3)	..
Change from baseline	0.2 (3.5)	1.1 (4.4)	..	-1.9 (3.1)	-0.6 (3.6)	..
Systolic blood pressure, mm Hg	..	..	-6.89 (-17.2 to 3.44); p=0.49	..	..	-2.54 (-11.8 to 6.72); p=0.85
Week 0	138.1 (11.7)	138.1 (14.5)	..	127.2 (11.1)	136.3 (14.0)	..
Week 14	139.0 (17.2)	131.4 (10.4)	..	125.2 (11.2)	127.8 (14.6)	..
Change from baseline	-0.3 (15.1)	-7.6 (9.4)	..	-1.4 (11.3)	-8.5 (12.3)	..
Diastolic blood pressure, mm Hg	..	..	-5.27 (-10.52 to -0.04); p=0.31	..	..	-0.52 (-5.02 to 3.98); p=0.95
Week 0	79.1 (5.7)	78.5 (6.8)	..	79.4 (8.3)	81.5 (6.5)	..
Week 14	81.7 (7.2)	76.8 (5.3)	..	78.4 (9.4)	79.9 (7.8)	..
Change from baseline	2.0 (7.5)	-3.9 (3.0)	..	-0.4 (5.8)	-1.6 (6.2)	..
Heart rate, beats per minute	..	..	3.98 (-2.62 to 10.59); p=0.55	..	..	-1.21 (-6.94 to 4.53); p=0.89
Week 0	66.1 (6.7)	67.7 (10.7)	..	72.0 (9.1)	73.0 (8.4)	..
Week 14	63.9 (6.7)	70.0 (16.8)	..	75.7 (9.9)	75.7 (6.9)	..
Change from baseline	-2.5 (8.1)	0.5 (10.3)	..	3.7 (8.5)	2.7 (6.3)	..

Data are mean (SD), unless stated otherwise. Change from baseline (week 0) was calculated in relation to week 14 for each participant and reported as a group mean, ignoring missing values. Estimated treatment differences do not directly correspond to observed mean changes, as they are model-based estimates adjusted for baseline values and implicitly account for missing data through maximum likelihood estimation. Efficacy analyses included baseline data from all participants and follow-up data from those on-treatment, with missing data after treatment or study discontinuation handled implicitly by maximum likelihood estimation in the constrained linear mixed model (used for repeated measures). p values were adjusted for multiple testing using Bonferroni correction (primary endpoint) or Benjamini-Hochberg method (secondary endpoints). There were 15 participants at baseline and 14 at week 14 in the placebo plus placebo group, 16 at baseline and eight at week 14 in the placebo plus GIP group, 15 at baseline and 14 at week 14 in the semaglutide plus placebo group, and 15 at baseline and week 14 in the semaglutide plus GIP group. GIP=glucose-dependent insulinotropic polypeptide.

Table 2: Primary and secondary outcomes at baseline and week 14 (end of treatment; efficacy population)

primary and secondary analyses included baseline data from all randomly assigned participants and follow-up data until treatment or study discontinuation targeting an efficacy estimand. Missing data were implicitly handled by a constrained linear mixed model¹⁹ including time (baseline vs follow-up) and constrained time-treatment interaction as fixed effect and with a shared unstructured covariance pattern to account for repeated measurements for each participant.

Models were fitted with R-package LMMstar (version 1.1.0) using restricted maximum likelihood estimation and with denominator degrees of freedom calculated using Satterthwaite approximation (package defaults). Estimated treatment differences were reported as baseline adjusted mean differences for GIP plus placebo versus placebo plus placebo and semaglutide plus GIP versus semaglutide plus placebo, except from substantially skewed outcomes which were log transformed before analysis and reported as baseline adjusted ratios in geometric means and mean differences in fasting concentrations of GIP at follow-up evaluated using Welch's *t* test. The primary endpoints were reported with 97.5% CIs and p values adjusted for multiple testing using Bonferroni correction, which controls the family-wise error rate at the 5% significance level. The secondary endpoints were reported with 95% CI and p values adjusted for multiple testing using the method of Benjamini and Hochberg, which control the false discovery rate.²⁰

Post-hoc analysis using the per-protocol population of the primary endpoint were conducted due to an uneven distribution of study discontinuations between treatment groups in those who completed the study and were identical to the primary analysis. Post-hoc safety analysis was carried out on request of reviewers including all randomly assigned participants regardless of treatment or study continuation and was done with pairwise comparisons of three active treatment groups with placebo plus placebo reported as risk differences and Wilson 95% CI, as implemented in R package DescTools (version 0.99.60). R (version 4.4.1) was used for data management and descriptive statistics. Data collection and management were performed using the REDCap electronic data capture system with all files stored on encrypted access-controlled institutional servers following applicable data protection regulations.

Role of the funding source

The funder had a role in reading and commenting on the protocol and report, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 31, 2022, and Sept 4, 2024, we assessed 134 individuals with type 2 diabetes for eligibility, of whom 73 were ineligible. We enrolled and randomly

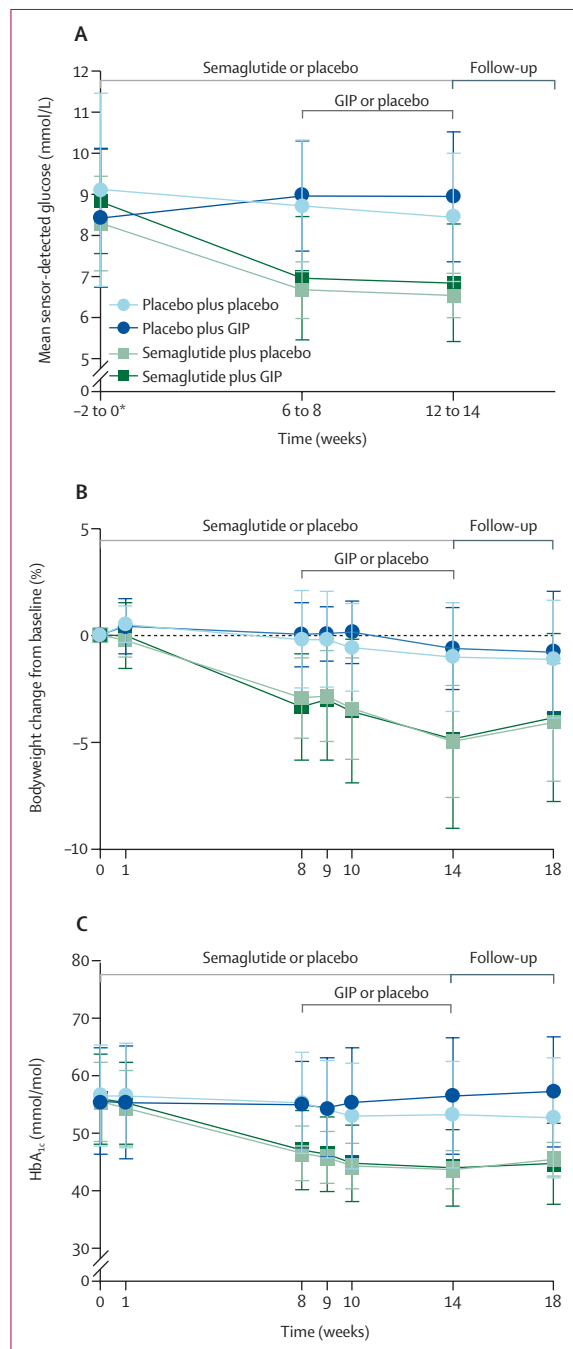


Figure 2: 14-day mean sensor-detected glucose (A), bodyweight change from baseline (B), and HbA_{1c} (C) in the efficacy population
Bars show mean (SD). The dashed line represents baseline levels. Glucose was assessed by continuous glucose monitoring. There were 15 participants at baseline and 14 at week 14 in the placebo plus placebo group, 16 at baseline and eight at week 14 in the placebo plus GIP group, 15 at baseline and 14 at week 14 in the semaglutide plus placebo group, and 15 at baseline and week 14 in the semaglutide plus GIP group. GIP=glucose-dependent insulinotropic polypeptide. *Timepoint represents the baseline measurement period of 14 days before starting treatment.

assigned 61 participants (15 to placebo plus placebo, 16 to placebo plus GIP, 15 to semaglutide plus placebo, and 15 to semaglutide plus GIP; efficacy population; figure 1). Baseline clinical characteristics were similar between the groups (table 1). Participants had a median HbA_{1c} of 54.0 mmol/mol (IQR 49.0–60.0), diabetes duration of 6.3 years (4.2–9.8), and a mean BMI of 31.6 kg/m² (SD 4.8). The median age was 64.0 years (IQR 60.0–68.0). 22 (36%) participants were female and 39 (64%) were male; all self-reported as White European (recruited in Denmark).

Ten (16%) of 61 participants discontinued the study and 51 (84%) were included in the per protocol population. Reasons for withdrawal were technical difficulties with the infusion pump with reports that operating the device required substantial effort, including frequent infusion-set changes and vial refilling (five in the placebo plus GIP and one in the placebo plus placebo groups); adverse events (two injection site reactions and one episode of diarrhoea before GIP initiation in the placebo plus GIP group); and personal reasons (one in semaglutide plus placebo). Repeated pump alarms were mainly caused by kinking of the infusion line or increased flow resistance (probably related to local injection site reactions).

The estimated effect of GIP on change in 14-day mean sensor-detected glucose from baseline to end of treatment was 0.80 mmol/L (97.5% CI –0.18 to 1.80; $p=0.13$ in the placebo plus GIP vs placebo plus placebo groups) and 0.05 mmol/L (–0.85 to 0.95; $p=1.00$ in the semaglutide plus GIP vs semaglutide plus placebo groups; table 2; figure 2). In a post-hoc analysis, the estimated effect of GIP on change in 14-day mean sensor-detected glucose from baseline to end of treatment was 0.62 mmol/L (–0.46 to 1.70; $p=0.18$ in the placebo plus GIP vs placebo plus placebo groups) and 0.03 mmol/L (–0.89 to 0.94; $p=0.95$ in the semaglutide plus GIP vs semaglutide plus placebo groups). Treatment with GIP increased plasma concentrations of intact and total GIP (figure 3). Fasting concentrations of intact (bioactive) GIP at the end of treatment on week 14 were mean 7 pmol/L (SD 4) in the placebo plus placebo group, 45 pmol/L (43) in the placebo plus GIP group, 10 pmol/L (6) in the semaglutide plus placebo group, and 85 pmol/L (92) in the semaglutide plus GIP group; whereas fasting concentrations of total GIP at the end of treatment were 14 pmol/L (7), 375 pmol/L (377), 18 pmol/L (19), and 527 pmol/L (338), respectively.

There were no statistically significant effects of GIP infusion on fasting plasma glucagon and plasma glucose concentrations between the primary comparison groups (table 2). For glycaemic variability, time in glycaemic ranges, HbA_{1c}, bodyweight, waist circumference, systolic blood pressure, diastolic blood pressure, and heart rate there were no significant differences between the primary comparison groups (table 2; figure 2; appendix pp 21–22).

From the OGTT, there were no significant differences in change from baseline to end of treatment of fasting plasma glucose concentrations, maximum plasma glucose concentrations, time to maximum glucose concentrations, glucose AUC, insulin outcomes, C-peptide outcomes, β -cell responsiveness (appendix p 3), or paracetamol absorption rate (data not shown).

Aside from any gastrointestinal event, injection site reactions were the most common adverse event (seven [44%] of 16 with placebo plus GIP, 11 [73%] of 15 with semaglutide plus GIP, and two [13%] of 15 in both placebo groups; table 3). Reactions were typically mild to moderate and characterised by redness, swelling, itching, and soreness. Gastrointestinal adverse events were more frequent in semaglutide groups (nine [60%] with placebo plus placebo, 11 [69%] with placebo plus GIP, 11 [73%] with semaglutide plus placebo, and 12 [80%] with semaglutide plus GIP), whereas diarrhoea occurred in four (27%), six (38%), seven (47%), and three (20%) participants. There were no deaths during the trial. The timing of gastrointestinal adverse events is shown in the appendix (p 8). The post-hoc safety analysis of adverse events, including pairwise comparisons of each active treatment group versus the placebo plus placebo group, is summarised in the appendix (p 9).

Discussion

In this study, 6 weeks of subcutaneous GIP infusion as an add-on to semaglutide did not improve glycaemic control at the prespecified target of 1.50 mmol/L. Due to dropouts, we cannot draw firm conclusions on the effects of GIP as add-on to placebo. GIP had no statistically significant effect on other glycaemic outcomes (glucose variability, times in ranges, HbA_{1c}, and glucose excursions during OGTT), insulin, C-peptide, insulin sensitivity, or β -cell responsiveness in individuals with type 2 diabetes. Furthermore, GIP did not affect bodyweight, waist circumference, systolic and diastolic blood pressure, heart rate, or fasting plasma concentrations of glucagon.

For the effects of GIP as add-on to placebo, the small number of participants who completed the study resulted in statistically uncertain estimates with wide CIs. Although non-statistically significant between-group differences were observed, the CI for the placebo plus GIP versus placebo plus placebo comparison of the primary endpoint was wide and included the prespecified target difference of 1.50 mmol/L; thus, clinically meaningful effects cannot be ruled out. The short trial timeframe allowed replacement of only one withdrawn participant. Sensitivity analyses were not feasible due to the small number of missing observations.

Adverse events were generally mild, with injection site reactions being the most frequent among participants who received GIP. Injection site reactions have been observed with tirzepatide, although at considerably lower frequencies (32 [9%] of 374 participants receiving tirzepatide vs one [<1%] of 376 receiving semaglutide)

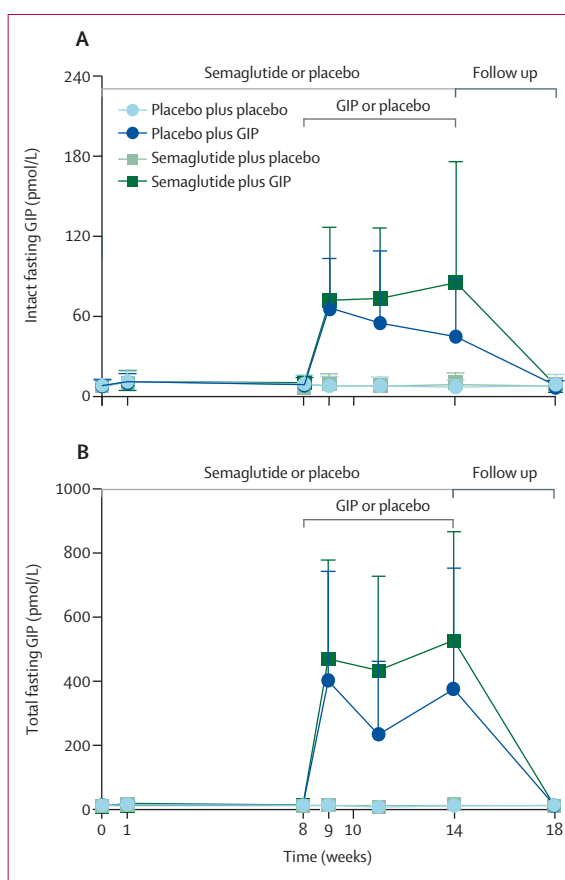


Figure 3: Plasma concentrations of intact GIP (1–42) (A) and total GIP (B) from baseline to follow-up in the efficacy population
Bars show mean (SD). There were 15 participants at baseline and 14 at week 14 in the placebo plus placebo group, 16 at baseline and eight at week 14 in the placebo plus GIP group, 15 at baseline and 14 at week 14 in the semaglutide plus placebo group, and 15 at baseline and week 14 in the semaglutide plus GIP group. GIP=glucose-dependent insulinotropic polypeptide.

than in our trial (13 [43%] of 30 in semaglutide groups). Nevertheless, their occurrence supports the possibility that GIP or GIP-receptor activation contributes to local subcutaneous irritation.²¹ The alkaline pH of the GIP solution might have also contributed. Gastrointestinal events were common, consistent with GLP-1 receptor agonist treatment.²¹ Although there was a higher overall frequency of gastrointestinal events with semaglutide, symptoms were heterogeneous with no clear pattern across groups. Gastrointestinal adverse effects were captured using participant self-reporting (a study diary), which might reduce the sensitivity and comparability of these assessments. No serious adverse events occurred.

The introduction of dual GIP and GLP-1 receptor agonists for individuals with type 2 diabetes highlights the need for understanding long-term metabolic effects of GIP. Our findings align with previous short-term infusion studies showing negligible insulinotropic or glucose-lowering effects of native GIP in this population.^{22,23} The insulinotropic effects of GIP can be

	Placebo plus placebo (n=15)	Placebo plus GIP (n=16)	Semaglutide plus placebo (n=15)	Semaglutide plus GIP (n=15)	Total (n=61)
Adverse events					
Injection site reaction to pump	2 (13%); 3; 0	7 (44%); 11; 2	2 (13%); 6; 0	11 (73%); 25; 0	22 (36%); 45; 2
Diarrhoea	4 (27%); 6; 0	6 (38%); 14; 1	7 (47%); 14; 0	3 (20%); 4; 0	20 (33%); 38; 1
Constipation	1 (7%); 2; 0	2 (13%); 2; 0	5 (33%); 16; 0	7 (47%); 13; 0	15 (25%); 33; 0
Decreased appetite	2 (13%); 3; 0	1 (6%); 1; 0	6 (40%); 10; 0	5 (33%); 11; 0	14 (23%); 25; 0
Viral respiratory tract infection	3 (20%); 3; 0	4 (25%); 8; 0	4 (27%); 5; 0	1 (7%); 1; 0	12 (20%); 17; 0
Abdominal pain	3 (20%); 3; 0	2 (13%); 2; 0	4 (27%); 4; 0	3 (20%); 4; 0	12 (20%); 13; 0
Nausea	3 (20%); 4; 0	0	3 (20%); 16; 0	5 (33%); 19; 0	11 (18%); 39; 0
Fatigue	3 (20%); 6; 0	2 (13%); 4; 0	3 (20%); 7; 0	2 (13%); 5; 0	10 (16%); 22; 0
Headache	3 (20%); 4; 0	2 (13%); 3; 0	3 (20%); 11; 0	2 (13%); 2; 0	10 (16%); 20; 0
Dizziness	1 (7%); 1; 0	4 (25%); 5; 0	2 (13%); 4; 0	2 (13%); 4; 0	9 (15%); 14; 0
Bloating	1 (7%); 5; 0	3 (19%); 3; 0	3 (20%); 5; 0	1 (7%); 2; 0	8 (13%); 15; 0
Dyspepsia	0	0	4 (27%); 14; 0	3 (20%); 5; 0	7 (11%); 19; 0
Hot flashes	0	0	4 (27%); 8; 0	2 (13%); 3; 0	6 (10%); 11; 0
Malaise	0	1 (6%); 1; 0	1 (7%); 1; 0	2 (13%); 8; 0	4 (7%); 10; 0
Gastroenteritis infection	0	1 (6%); 1; 0	1 (7%); 1; 0	2 (13%); 2; 0	4 (7%); 4; 0
Vomiting	1 (7%); 1; 0	0	2 (13%); 2; 0	1 (7%); 1; 0	4 (7%); 4; 0
Myalgia	1 (7%); 2; 0	0	2 (13%); 4; 0	0	3 (5%); 6; 0
Taste disorders	2 (13%); 3; 0	0	0	0	2 (3%); 3; 0
Back pain	0	2 (13%); 3; 0	0	0	2 (3%); 3; 0
Any event	8 (53%); 46; 0	9 (56%); 58; 3	13 (87%); 128; 0	13 (87%); 109; 0	38 (62%); 341; 3
Any gastrointestinal event	9 (60%); 24; 0	11 (69%); 22; 1	11 (73%); 81; 0	12 (80%); 59; 0	41 (67%); 186; 1
Serious adverse events	0	0	0	0	0

Data are n (%); events; events leading to study discontinuation. The safety population was all participants as randomly assigned regardless of treatment or study discontinuation. GIP=glucose-dependent insulintropic polypeptide.

Table 3: Adverse events occurring in at least 10% of participants in any treatment group (safety population)

restored in some circumstances. During acute intravenous GIP infusion in participants with type 2 diabetes, a modest but statistically significant increase in C-peptide response was observed after 4 weeks of near-normalisation of blood glucose with insulin therapy.¹¹ These findings were attributed to improved glycaemic control and induced by approximately three times lower plasma GIP concentrations (mean 132 pmol/L) than obtained in our study (mean 527 pmol/L in the semaglutide plus GIP group). In our study, the improvement in glycaemic control reached with 8 weeks of semaglutide did not alter the glycaemic effects of GIP. One explanation for this discrepancy is that the previous assessment of the insulintropic effect of GIP was based on a hyperglycaemic clamp at 15.0 mmol/L combined with GIP infusion, which likely elicited a stronger β -cell response than the OGTT used in our protocol. In addition, restoration of GIP-related glycaemic effects might depend on the duration of diabetes and degree of glycaemic control. In our study, the median diabetes duration was 7.9 years (SD 5.9; median 6.3 years [IQR 4.2–9.8]) compared with 4.5 years (3.6) in the previous study.¹¹ Furthermore, baseline mean HbA_{1c} in the previous study was 8.6% (1.3), whereas our participants had a lower median HbA_{1c} of 7.1% (6.6–7.6), which possibly limited the

scope for glycaemic improvement and attenuating effects of GIP.

To our knowledge, our study is the first to explore the metabolic effects of long-term supraphysiological exposure to native GIP in humans. Previously, the longest exposure was 6 days of continuous subcutaneous infusion in individuals with type 1 diabetes and the longest exposure in general was an intravenous infusion for 360 min.^{24,25} A strength of our study is the randomised, double-blind, placebo-controlled, and parallel design, which minimised the detection bias by applying double-blinded CGM measurements for the primary outcome. Our study provides the opportunity to compare metabolic effects of long-term supraphysiological GIP receptor activation in people with type 2 diabetes who received or did not receive a GLP-1 receptor agonist (semaglutide).

We did not reach the estimated sample size to achieve the predefined statistical power. Although 61 participants were randomly assigned, ten discontinued mostly due to pump-related technical issues and injection site reactions. Missing data due to participant withdrawal reduced the precision of our estimated treatment effects, particularly for the placebo plus GIP versus placebo plus placebo comparison. As only one participant could be replaced within the study timeline, the smaller sample size increased uncertainty around the point estimates.

This limitation affects the robustness of our conclusions regarding the magnitude of this treatment effect. Some participants who completed the study also had pump malfunctions, possibly leading to periods without functional pump infusion. These issues might have contributed to the large SDs of the GIP concentrations observed in groups who received GIP. Consequently, the placebo plus GIP versus placebo plus placebo comparison is underpowered and the modest sample size should be considered when interpreting these analyses. Nonetheless, both groups who received GIP reached supraphysiological fasting GIP concentrations and a post-hoc analysis of the primary endpoint (excluding participants who discontinued) was consistent with the primary analysis. The combination of a small sample size and high interindividual variability means that our findings should be interpreted with caution. Furthermore, the study population was ethnically homogeneous, which might reduce the generalisability of our findings. Additionally, the prespecified minimal relative difference of 1.50 mmol/L probably exceeded the short-term effect size expected from native GIP add-on over 6 weeks, further reducing the power to detect smaller differences.

Another possible limitation is whether the chosen infusion rate of GIP (16 pmol/kg per min) was sufficient to confer relevant metabolic effects when administered subcutaneously. This infusion rate was selected due to being the highest reported and well tolerated intravenous infusion dose of GIP according to our review of previous literature on adverse reactions to exogenous GIP.²⁶ Notably, subcutaneously administered GIP probably has lower bioavailability than intravenous GIP, similar to the observation for GLP-1, indicating that a portion of the active hormone is degraded before reaching the circulation.²⁷ Additionally, the resulting circulating concentrations varied between timepoints and between individuals, and whether the GIP treatment period of 6 weeks was sufficient to provide a clinically relevant glycaemic effect is worth considering; however, this duration was the maximum practically possible. Despite these limitations in dose and duration, we did expect some effect on glucose concentrations after 6 weeks. In the SURPASS-2 trial, the efficacy of a dual GIP and GLP-1 receptor agonist tirzepatide versus semaglutide in individuals with type 2 diabetes was associated with reductions in HbA_{1c} and fasting plasma glucose between tirzepatide and semaglutide by 6 weeks. Although statistical significance at 6 weeks was not reported, the results suggest a numerical difference between treatment groups at this timepoint.²⁸

Considering the notable effects of dual GIP and GLP-1 receptor agonists on blood glucose and bodyweight in individuals with type 2 diabetes, the absence of treatment effects from long-term exposure to exogenous GIP might seem surprising; however, comparing the effects of native GIP to those of highly optimised therapeutic

molecules with enhanced receptor affinity and optimised pharmacodynamic and pharmacokinetic properties is challenging. For example, any GIP receptor-mediated effects of tirzepatide might be due to the particular properties of that peptide. Tirzepatide reaches circulating concentrations that are 15–28 times higher than native GIP concentrations reached in our study, and its binding to albumin prolongs half-life and might enhance central appetite-regulating effects.²⁹ Factors that likely contribute to markedly greater metabolic efficacy of tirzepatide compared with native GIP infusion used in our study. The significant effects of tirzepatide possibly arise from biased agonism at the GLP-1 receptor, which is characterised by reduced β -arrestin recruitment with tirzepatide compared with native GLP-1 while maintaining robust cyclic AMP activation. This signalling profile promotes sustained receptor presence at the cell surface and enhances receptor activation.^{14,30} Due to a unimolecular structure, the distinct actions from each receptor have yet to be elucidated in humans. One trial has evaluated a long-acting GIP receptor monoagonist, showing reduced liraglutide-induced gastrointestinal adverse effects in 9 days, although this study was not powered to assess metabolic efficacy.³¹ These findings support the emerging interest in GIP receptor agonism, but robust efficacy data remain scarce.

Antagonising the GIP receptor might also be beneficial for management of plasma glucose and bodyweight. Another proposed explanation for the effects of tirzepatide is that GIP receptors at the cell surface become downregulated upon stimulation;³² thus, when the GIP receptor is continuously stimulated during tirzepatide treatment, tirzepatide acts as a functional antagonist of the receptor similarly to when the GIP receptor is stimulated with native GIP.³⁰ In a phase 2 study, a bispecific GIP receptor antagonist (receptor antibody) conjugated with two peptide-based GLP-1 receptor agonists, maridebart cafraglutide reduced bodyweight by 12.3% and HbA_{1c} by 1.6% in individuals with type 2 diabetes and obesity.³³

The mechanism by which GIP receptor agonism and antagonism exert appetite-regulating effects has been investigated in rodent models,³⁴ which suggest that GIP receptor agonists and antagonists (with undisclosed pharmacodynamic profiles) act through different pathways in appetite-regulating areas of the brain that both reduce energy intake. Whether these mechanisms translate in the human brain remains unknown and, in our study, we did not observe any weight-lowering effects of GIP.

In summary, 6 weeks of subcutaneous GIP infusion as add-on to placebo or semaglutide did not improve glycaemic control in individuals with type 2 diabetes at the prespecified target of 1.50 mmol/L. Our conclusions regarding the effects of GIP as add-on to placebo are limited by insufficient statistical power due to the high number of dropouts. Future studies should explore the

differential effects of isolated GIP receptor activation versus dual GIP and GLP-1 receptor agonism, particularly the optimisation of dosing and treatment duration.

Contributors

MMH, MBC, FKK, and LSG designed and initiated the study. MMH, CF-W, NLS, IWL, JJH, BH, AE, and LSG contributed to data collection and analysis. MMH and JLF performed the statistical analyses. MMH wrote the first draft of this manuscript. CKN was responsible for randomisation and allocation of study medication. ABL, FKK, TV, and LSG supervised the trial. All authors revised the original manuscript for crucial intellectual content. MMH and LSG verified the underlying data. MMH and LSG guarantee the integrity of data and the accuracy of data analyses. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

CF-W and IWL are shareholders of Novo Nordisk. ABL served on a scientific advisory panel for Eli Lilly; and received speaker honoraria from Boehringer Ingelheim, Novo Nordisk, and Zealand Pharma. JJH is a cofounder and shareholder of Antag Therapeutics; and served on scientific advisory panels or received speaker honoraria (or both) from AlphaSights, Eli Lilly, Novo Nordisk, MSD, Structure Therapeutics, and Zealand Pharma. TV served on scientific advisory panels, speakers' bureaus, and was a consultant or received research support (or both) from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, MSD, Novo Nordisk, Sanofi, and Sun Pharma. FKK served on scientific advisory panels, speaker's bureaus, was a consultant, owns stocks or received research support (or both) from 89bio, Amgen, AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, MedImmune, MSD, Norgine, Novo Nordisk, Sanofi, ShouTi, SNIPR Biome, Zealand Pharma, and Zucara; and is a cofounder and shareholder in Antag Therapeutics. TV, CKN, and FKK are employed by Novo Nordisk. LSG received a grant from Novo Nordisk Foundation (NNF18SA0034956); is a shareholder and cofounder of Antag Therapeutics; and reports receiving a personal lecture fee from Novo Nordisk. All other authors declare no competing interests.

Data sharing

All data are owned by the Capital Region of Denmark and investigators. Data underlying this study will be available from the corresponding author (lsg@sund.ku.dk) upon reasonable request.

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