



Clinical trial results:

The separate and combined effects of long-term GIP and GLP-1 receptor activation in patients with type 2 diabetes

Summary

EudraCT number	2020-004774-22
Trial protocol	DK
Global end of trial date	06 January 2025

Results information

Result version number	v1 (current)
This version publication date	03 July 2026
First version publication date	03 July 2026
Summary attachment (see zip file)	Helsted et al. 2026 (Helsted et al. 2026.pdf)

Trial information

Trial identification

Sponsor protocol code	GIP-SEMA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05078255
WHO universal trial number (UTN)	U1111-1259-1491

Notes:

Sponsors

Sponsor organisation name	Center for Clinical Metabolic Research
Sponsor organisation address	Gentofte Hospitalsvej 7, Hellerup, Denmark, 2900
Public contact	Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, +45 3867 2461, Asger.Lund.01@regionh.dk
Scientific contact	Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, +45 3867 2461, Asger.Lund.01@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2025
Global end of trial reached?	Yes
Global end of trial date	06 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The present study will evaluate the glucose-lowering effect (assessed by continuous glucose monitoring (CGM)) of the native hormone GIP in the context of pharmacological GLP-1 receptor activation in patients with type 2 diabetes. We hypothesise that long-term GLP-1 receptor agonism during concomitant GIP receptor agonism will disclose new physiological insights into glucose homeostasis and body weight regulation that may be used therapeutically in the future.

Protection of trial subjects:

Subjects kept a trial diary where adverse effects were documented. At safety visits during the trial, the diary was assessed and a medical examination conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January 31, 2022, and September 4, 2024, we assessed 134 individuals for eligibility and enrolled 61 participants, who were randomly assigned to treatment regimens: 15 participants, placebo + placebo; 16 participants, placebo + GIP; 15 participants, semaglutide + placebo; 15 participants, semaglutide + GIP.

Pre-assignment

Screening details:

Inclusion criteria: 18-74 years of age; type 2 diabetes for at least six months; stable treatment with diet and exercise and/or any combination of stable treatment with metformin, sodium-glucose cotransporter 2 inhibitors, DPP-4 inhibitors, and sulphonylurea; glycated haemoglobin A1C of 6.5-10.5%; body mass index of 25-50 kg/m²; stable body weight.

Period 1

Period 1 title	Baseline (before intervention)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study is a double-blinded, randomised (1:1:1:1), placebo-controlled, clinical trial.

Arms

Are arms mutually exclusive?	Yes
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Arm title	1) placebo + placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	No treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

None - No treatment.

Arm title	2) placebo + GIP
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	No treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

None - No treatment.

Arm title	3) semaglutide + placebo
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	No treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

None - No treatment.

Arm title	4) semaglutide + GIP
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	No treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

None - No treatment.

Number of subjects in period 1	1) placebo + placebo	2) placebo + GIP	3) semaglutide + placebo
Started	15	16	15
Completed	15	16	15

Number of subjects in period 1	4) semaglutide + GIP
Started	15
Completed	15

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The study is a double-blinded, randomised (1:1:1:1), placebo-controlled, clinical trial.

Arms

Are arms mutually exclusive?	Yes
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Arm title	1) placebo + placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
same as active	
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
same as active comparator	
Arm title	2) placebo + GIP
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	glucose-dependent insulinitropic polypeptide 1-42
Investigational medicinal product code	
Other name	GIP
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
16 pmol/kg/min continuous subcutaneous infusion for six weeks	
Investigational medicinal product name	saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
same as active	
Arm title	3) semaglutide + placebo
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	semaglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details:	
0.5 mg once weekly subcutaneous injection	
Arm title	4) semaglutide + GIP
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	semglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
0.5 mg once weekly subcutaneous injection	
Investigational medicinal product name	glucose-dependent insulintropic polypeptide 1-42
Investigational medicinal product code	
Other name	GIP
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use
Dosage and administration details:	
16 pmol/kg/min continuous subcutaneous infusion for six weeks	

Number of subjects in period 2	1) placebo + placebo	2) placebo + GIP	3) semaglutide + placebo
Started	15	16	15
Completed	14	8	14
Not completed	1	8	1
Consent withdrawn by subject	1	8	1

Number of subjects in period 2	4) semaglutide + GIP
Started	15
Completed	15
Not completed	0
Consent withdrawn by subject	-

Baseline characteristics

Reporting groups

Reporting group title	Baseline (before intervention)
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Reporting group description: -

Reporting group values	Baseline (before intervention)	Total	
Number of subjects	61	61	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	29	29	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	39	39	

End points

End points reporting groups

Reporting group title	1) placebo + placebo
Reporting group description: -	
Reporting group title	2) placebo + GIP
Reporting group description: -	
Reporting group title	3) semaglutide + placebo
Reporting group description: -	
Reporting group title	4) semaglutide + GIP
Reporting group description: -	
Reporting group title	1) placebo + placebo
Reporting group description: -	
Reporting group title	2) placebo + GIP
Reporting group description: -	
Reporting group title	3) semaglutide + placebo
Reporting group description: -	
Reporting group title	4) semaglutide + GIP
Reporting group description: -	

Primary: Change in 14-day mean glucose levels

End point title	Change in 14-day mean glucose levels
End point description: For the primary endpoint, mean changes of sensor-detected glucose from baseline to end-of-treatment for the two primary comparisons were similar. The effects of treatment with GIP regarding mean sensor-detected glucose from baseline to end-of-treatment were estimated to 0.80 mmol/L (97.5% CI 0.18 to 1.80, p=0.13) (placebo + GIP vs. placebo + placebo) and 0.05 mmol/L (97.5% CI -0.85 to 0.95, p=1.00) (semaglutide + GIP vs. semaglutide + placebo), respectively.	
End point type	Primary
End point timeframe: The primary endpoint is change in 14-day mean glucose levels (assessed by blinded CGM) during the last 14 days of the intervention period as compared to 14-day mean glucose levels during the last 14 days of the run-in period.	

End point values	1) placebo + placebo	2) placebo + GIP	3) semaglutide + placebo	4) semaglutide + GIP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	15	15
Units: mmol/L				
arithmetic mean (standard deviation)	9.1 (± 2.4)	8.4 (± 1.7)	8.3 (± 1.2)	8.8 (± 1.3)

End point values	1) placebo + placebo	2) placebo + GIP	3) semaglutide + placebo	4) semaglutide + GIP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	15	15

Units: mmol/L				
arithmetic mean (standard deviation)	8.4 ($\pm$ 1.6)	8.9 ($\pm$ 1.6)	6.5 ($\pm$ 0.5)	6.8 ($\pm$ 1.4)

Statistical analyses

Statistical analysis title	constrained linear mixed model
Comparison groups	4) semaglutide + GIP v 1) placebo + placebo v 2) placebo + GIP v 3) semaglutide + placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	$\leq$ 97.5
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)

Secondary: Secondary endpoints - Glycaemic variability

End point title	Secondary endpoints - Glycaemic variability
End point description:	For glycaemic variability (coefficient of variance of CGM measurements), time in glycaemic ranges, HbA1C, body weight, waist circumference, systolic blood pressure, and heart rate there were no differences regarding the two primary comparisons.
End point type	Secondary
End point timeframe:	Glycaemic variability will be assessed by 14-day coefficient of variance (CV) of glucose levels (assessed by CGM) during the last 14 days of the intervention period as compared to 14-day CV of glucose levels during the last 14 days of the run-in period.

End point values	1) placebo + placebo	2) placebo + GIP	3) semaglutide + placebo	4) semaglutide + GIP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	15	15
Units: %				
number (not applicable)	22	22	21	22

End point values	1) placebo + placebo	2) placebo + GIP	3) semaglutide + placebo	4) semaglutide + GIP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	15	15
Units: %				
number (not applicable)	22	21	18	20

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Adverse event reporting additional description:

The most common adverse event was injection site reaction to the GIP infusion. The injection site reaction was an inflammatory response localised to the injection site, characterised by redness, swelling, itching, and soreness. The severity of the reaction varied between participants but was generally mild to moderate.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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Reporting groups

Reporting group title	Placebo + placebo
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Reporting group description: -

Reporting group title	Placebo + GIP
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Reporting group description: -

Reporting group title	Semaglutide + placebo
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Reporting group description: -

Reporting group title	Semaglutide + GIP
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Reporting group description: -

Serious adverse events	Placebo + placebo	Placebo + GIP	Semaglutide + placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Semaglutide + GIP		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo + placebo	Placebo + GIP	Semaglutide + placebo
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 15 (53.33%)	9 / 16 (56.25%)	11 / 15 (73.33%)
General disorders and administration site conditions Injection site reaction to pump subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3	7 / 16 (43.75%) 11	2 / 15 (13.33%) 6
Gastrointestinal disorders Any gastrointestinal adverse event subjects affected / exposed occurrences (all)	8 / 15 (53.33%) 24	9 / 16 (56.25%) 22	11 / 15 (73.33%) 81

Non-serious adverse events	Semaglutide + GIP		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 15 (80.00%)		
General disorders and administration site conditions Injection site reaction to pump subjects affected / exposed occurrences (all)	11 / 15 (73.33%) 25		
Gastrointestinal disorders Any gastrointestinal adverse event subjects affected / exposed occurrences (all)	12 / 15 (80.00%) 59		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/42173109>

<http://www.ncbi.nlm.nih.gov/pubmed/36849212>