Clinical trial results:
Low-dose glucagon for Prevention of Exercise-Induced Hypoglycemia in People with Type 1 Diabetes

Summary

EudraCT number	2021-001342-34
Trial protocol	DK
Global end of trial date	31 August 2023

Results information

Result version number	v1 (current)
This version publication date	27 November 2024
First version publication date	27 November 2024

Trial information

Trial identification

Sponsor protocol code	78618

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	Borgmester Ib Juuls Vej 89, Herlev, Denmark, 2730
Public contact	Sissel Lundemose, Steno Diabetes Center Copenhagen, +45 23742764, sissel.lundemose@regionh.dk
Scientific contact	Sissel Lundemose, Steno Diabetes Center Copenhagen, +45 23742764, sissel.lundemose@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	31 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2023
Global end of trial reached?	Yes
Global end of trial date	31 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the efficacy of single-administration low-dose (150 µg) s.c. glucagon and split-administration low-dose (2 x 75 µg) s.c. glucagon to placebo for prevention of exercise-induced hypoglycemia in people with type 1 diabetes using insulin pumps and multiple daily injections (MDI).

Protection of trial subjects:

NA

Background therapy:

All participants used their regular treatment modality; 11 participants used insulin pump therapy and 11 participants used MDI therapy.

Evidence for comparator:

-

Actual start date of recruitment	02 August 2021
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	17

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the outpatient diabetes clinic at Steno Diabetes Center Copenhagen from November 2021 to June 2023.

Pre-assignment

Screening details:

After providing oral and written informed consent, participants completed a screening visit for assessment of the eligibility criteria. Procedures included routine blood sampling, physical examination, review of medical history and medications as well as registration of baseline characteristics.

Period 1

Period 1 title	Study period overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

The study was a single-blind study. The participants were blinded to the intervention.

Arms

Are arms mutually exclusive?	No
Arm title	150 microgram glucagon

Arm description:

Pre-exercise 150 µg s.c. glucagon and post-exercise placebo

Arm type	Experimental
Investigational medicinal product name	GlucaGen
Investigational medicinal product code	SUB02347MIG
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Injection

Dosage and administration details:

150 microgram and s.c. injection

Arm title	75 microgram glucagon

Arm description:

Pre-exercise 75 µg s.c. glucagon and post-exercise 75 µg s.c. glucagon

Arm type	Experimental
Investigational medicinal product name	GlucaGen
Investigational medicinal product code	SUB02347MIG
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Injection

Dosage and administration details:

150 microgram and s.c. injection

Arm title	Placebo

Arm description:

Pre-exercise placebo and post-exercise placebo

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Injection

Dosage and administration details:

150-75 microgram of saline injected s.c.

Number of subjects in period 1	150 microgram glucagon	75 microgram glucagon	Placebo
Started	22	22	22
Completed	22	22	22

Baseline characteristics

Reporting groups

Reporting group title	Study period overall

Reporting group description: -

Reporting group values	Study period overall	Total	
Number of subjects	22	22	
Age categorical			
18-64 years 65-84 years			
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)	17	17	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous			
Units: years			
median	57		
full range (min-max)	22 to 79	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	16	16	
BMI			
Units: kilogram(s)/square metre			
median	26.3		
full range (min-max)	20.3 to 29.4	-	
Type 1 diabetes duration			
Units: Years			
median	30		
full range (min-max)	2 to 63	-	
HbA1C			
Units: mmol/l			
median	53		
full range (min-max)	42 to 66	-	
HbA1c			
Units: Percentage			
median	7.0		
full range (min-max)	6.0 to 8.2	-	
Total daily insulin dose			
Units: unit(s)			
median	39		

full range (min-max)	12 to 73	-	
Physical activities			
Units: METs/week			
median	2561		
full range (min-max)	240 to 13068	-	

End points

End points reporting groups	
Reporting group title	150 microgram glucagon
Reporting group description:	
Pre-exercise 150 µg s.c. glucagon and post-exercise placebo	
Reporting group title	75 microgram glucagon
Reporting group description:	
Pre-exercise 75 µg s.c. glucagon and post-exercise 75 µg s.c. glucagon	
Reporting group title	Placebo
Reporting group description:	
Pre-exercise placebo and post-exercise placebo	

Primary: Rate of hypoglycaemia (<3.9mmol/l)	
End point title	Rate of hypoglycaemia (<3.9mmol/l)
End point description:	

End point type	Primary
End point timeframe:	
During exercise and post exercise resting phase (0-180 min)	

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: N	7	5	6	

Statistical analyses

Statistical analysis title	Logistic mixed effects regression model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Regression, Logistic

Secondary: Time below range (<3.9 mmol/L)	
End point title	Time below range (<3.9 mmol/L)
End point description:	
Unit: percentage point	

End point type	Secondary
End point timeframe:	
From exercise to post exercise (0-180 min)	

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: percent				
arithmetic mean (standard error)	3.3 (± 5.6)	4.1 (± 8.7)	5.2 (± 9.7)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.359
Method	Mixed models analysis

Secondary: Time in range (3.9-10.0 mmol/L)	
End point title	Time in range (3.9-10.0 mmol/L)
End point description:	
Unit: percentage point	
End point type	Secondary
End point timeframe:	
From Exercise and post exercise (0-180 min)	

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: percent				
arithmetic mean (standard deviation)	63.9 (± 38.9)	60.0 (± 34.1)	82.7 (± 29.6)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed models analysis

Secondary: Time above range (>10.0 mmol/L)	
End point title	Time above range (>10.0 mmol/L)
End point description: Unit: Percentage point	
End point type	Secondary
End point timeframe: From exercise and post exercise (0-180 min)	

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: Percent				
arithmetic mean (standard error)	32.2 (± 41.3)	35.9 (± 36.4)	13.2 (± 30.2)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 150 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 75 microgram glucagon

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Mixed models analysis

Secondary: Time to hypoglycaemia

End point title	Time to hypoglycaemia

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise (0-180 min)

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: minute				
arithmetic mean (standard deviation)	80.0 (± 35.7)	46.0 (± 10.8)	47.5 (± 43.8)	

Statistical analyses

Statistical analysis title	Non parametric test
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	Friedmanns Non parametric test

Secondary: Change in plasma glucose over time

End point title	Change in plasma glucose over time

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise (o-180 min)

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: mmol/l				
arithmetic mean (standard deviation)	0.03 (± 2.0)	0.76 (± 2.9)	-0.08 (± 1.8)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.419
Method	Mixed models analysis

Secondary: Mean Plasma glucose

End point title	Mean Plasma glucose

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise (0-180 min)

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: mmol/l				
arithmetic mean (standard deviation)	10.1 (± 2.8)	10.8 (± 3.3)	8.8 (± 2.6)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Mixed models analysis

Statistical analysis title	Copy of Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.787
Method	Mixed models analysis

Statistical analysis title	Copy of Copy of Generalized linear mixed model
Comparison groups	150 microgram glucagon v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076
Method	Mixed models analysis

Statistical analysis title	Copy of Copy of Copy of Generalized linear mixe...
Comparison groups	Placebo v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Mixed models analysis

Secondary: Hyperglycaemic events	
End point title	Hyperglycaemic events

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise (0-180 min)

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: N	11	15	5	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.412
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Mixed models analysis

Secondary: Nadir

End point title	Nadir

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: mmol/l				
arithmetic mean (standard deviation)	6.6 (± 2.7)	7.0 (± 2.8)	6.0 (± 2.6)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223
Method	Mixed models analysis

Secondary: Peak

End point title	Peak

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise (0-180 min)

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: mmol/l				
arithmetic mean (standard deviation)	10.1 (± 2.8)	10.8 (± 3.3)	8.8 (± 2.6)	

Statistical analyses

Statistical analysis title	generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.511
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis

Secondary: Incemental peak	
End point title	Incemental peak
End point description:	

End point type	Secondary
End point timeframe:	
From exercise and post exercise (0-180 min)	

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: mmol/l				
arithmetic mean (standard deviation)	2.4 (± 1.4)	2.7 (± 1.9)	1.2 (± 1.4)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: AUC

End point title	AUC

End point description:

End point type	Secondary

End point timeframe:

From exercise and post exercise

End point values	150 microgram glucagon	75 microgram glucagon	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	22	
Units: mmol/l*min				
arithmetic mean (standard deviation)	1565.5 (± 542.8)	1720.9 (± 584.5)	1357.3 (± 497.0)	

Statistical analyses

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	150 microgram glucagon v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	Mixed models analysis

Statistical analysis title	Generalized linear mixed model
Comparison groups	Placebo v 75 microgram glucagon
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From intervention (t=0) to the end of the observation period (t=180 min)

Adverse event reporting additional description:

Adverse effects (nausea, headache, stomachache, palpitations and injection site pain) were scored using a 0-100 visual analog scale (VAS) just prior to the intervention (t=0), after exercise (t=60 min) and two hours later (t=180) to evaluate whether any adverse events had occurred within three/two hours after the intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	150 microgram glucagon (G150)
Reporting group description: -	
Reporting group title	75*2 microgram glucagon (G75*2)
Reporting group description: -	
Reporting group title	Placebo (PBO)
Reporting group description: -	

Serious adverse events	150 microgram glucagon (G150)	75*2 microgram glucagon (G75*2)	Placebo (PBO)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	150 microgram glucagon (G150)	75*2 microgram glucagon (G75*2)	Placebo (PBO)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	5 / 22 (22.73%)	7 / 22 (31.82%)
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	1 / 22 (4.55%)
occurrences (all)	2	1	1
General disorders and administration site conditions			

Headache			
subjects affected / exposed	4 / 22 (18.18%)	3 / 22 (13.64%)	5 / 22 (22.73%)
occurrences (all)	5	4	11
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1

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