Clinical trial results:
Dual-Hormone Closed-Loop Glucose Control in Type 1 Diabetes

Summary

EudraCT number	2019-001631-31
Trial protocol	DK
Global end of trial date	19 March 2021

Results information

Result version number	v1 (current)
This version publication date	15 March 2023
First version publication date	15 March 2023
Summary attachment (see zip file)	Oral_presentation_ADA2021 (ADA 2021_Ranjan.pdf)

Trial information

Trial identification

Sponsor protocol code	DHCL2019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04053712
WHO universal trial number (UTN)	-
Other trial identifiers	Former EUDRA-CT: 2014-003261-20, Former Protocol code number: DHCL2014

Notes:

Sponsors

Sponsor organisation name	Steno Diabetes Center Copenhagen
Sponsor organisation address	Niels Steensens Vej 2, Gentofte, Denmark, 2820
Public contact	Ajenthen Ranjan, Steno Diabetes Center Copenhagen, +45 26196604, ajenthen.ranjan@regionh.dk
Scientific contact	Ajenthen Ranjan, Steno Diabetes Center Copenhagen, +45 26196604, ajenthen.ranjan@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	27 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2021
Global end of trial reached?	Yes
Global end of trial date	19 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aims of this two-phase project are to 1) demonstrate proof-of-concept and 2) to compare dual-hormone with single-hormone closed-loop glucose control.

Protection of trial subjects:

Participants experiencing symptomatic hypoglycemia or a plasmaglucose (PG) <3.0 mmol/L (54 mg/dL) received 15 g oral glucose (dextrose tablets) rescue treatment and received another if not resolved after 15 minutes. In contrast, if PG remained > 16.0 mmol/L (288 mg/dL) for two hours despite solving any closed-system malfunctions, an insulin bolus was administered based on the participant's insulin sensitivity factor (ISF) to aim for a PG of 7.0 mmol/L (126 mg/dL).
Side effects to glucagon (nausea, headache, stomachache, and palpitations) were scored using a 0–100 visual analog scale (VAS) every four hours from 7AM to 11PM.
Regardless of the mode of closed-loop control, the study visit lasted for 33 hours. The study pumps and the continuos glucose monitors (CGMs) were then disconnected and the participants were allowed to reconnect their own pump and CGM.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the outpatient clinic at Steno Diabetes Center Copenhagen, Denmark, from August 2019 to December 2020.

Pre-assignment

Screening details:

Inclusion criteria were age ≥18 years, T1D duration > 2 years, use of insulin pumps for ≥ 1 years, glycated hemoglobin (HbA1c) level ≤ 8.5% (69 mmol/mol), and current use of faster insulin aspart (Novo Nordisk, Bagsværd, Denmark).

Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	13

Period 1

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

Blinding implementation details:

The pumps were filled with FiAsp® and GlucaGen® during the DHCL visit or filled with FiAsp® and isotonic saline during SHCL, respectively. Participants were masked for the contents in the pumps.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dual-hormone --> Single hormone

Arm description:

Participants went through Dual-hormone and then Single-hormone treatment

Arm type	Experimental
Investigational medicinal product name	GlucaGen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Variable dose between 0-1mg given based on an algorithm for the treatment and prevention of hypoglycemia.

Investigational medicinal product name	Fiasp
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Injection

Dosage and administration details:

Variable dose given by the insulin pump

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection

Routes of administration	Injection

Dosage and administration details:

Saline was stored in an insulin pump but did not deliver any saline during the trials (e.g. functioned as a dummy-pump)

Arm title	Single-hormone --> Dual-hormone

Arm description:

Participants went through single-hormone and then dual-hormone treatment

Arm type	Experimental
Investigational medicinal product name	Fiasp
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Injection

Dosage and administration details:

Variable dose given by the insulin pump

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

Dosage and administration details:

Saline was stored in an insulin pump but did not deliver any saline during the trials (e.g. functioned as a dummy-pump)

Investigational medicinal product name	GlucaGen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Variable dose between 0-1mg given based on an algorithm for the treatment and prevention of hypoglycemia.

Number of subjects in period 1	Dual-hormone --> Single hormone	Single-hormone --> Dual-hormone
Started	7	6
Completed	7	6

Baseline characteristics

Reporting groups	
Reporting group title	Dual-hormone --> Single hormone
Reporting group description:	
Participants went through Dual-hormone and then Single-hormone treatment	
Reporting group title	Single-hormone --> Dual-hormone
Reporting group description:	
Participants went through single-hormone and then dual-hormone treatment	

Reporting group values	Dual-hormone --> Single hormone	Single-hormone --> Dual-hormone	Total
Number of subjects	7	6	13
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	57	47	
full range (min-max)	26 to 64	35 to 60	-
Gender categorical Units: Subjects			
Female	3	4	7
Male	4	2	6
Diabetes duration Units: year			
median	30.5	25	
full range (min-max)	17 to 40	19 to 45	-
Body mass index Units: kilogram(s)/square metre			
median	27.8	28.9	
full range (min-max)	22.2 to 36.6	22.2 to 36.5	-

Subject analysis sets	
Subject analysis set title	DHCL
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Data were analyzed in an intention-to-treat approach including periods with any malfunction of the infusion set (e.g. occlusions, kinking of the tube), missing CGM values, and loss of connectivity between study devices to run the closed-loop systems .	

Repeated-measures ANOVA with a compound symmetry covariance structure was used to test the differences between the two study visits, adjusting for the study order. If data had a skewed distribution, logarithmic transformations were used. If the transformations could not normalize the distribution, nonparametric Wilcoxon signed rank tests were used. Spearman correlations were used to determine relationships. The difference of the time course of PG, insulin and glucagon was tested with a linear mixed model with random effects. A P value of <0.05 was considered statistically significant. Non-predefined outcomes were Bonferroni adjusted for multiple comparisons within each parameter.

Subject analysis set title	SHCL
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Completers of SIngle-hormone

Reporting group values	DHCL	SHCL	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	50	50	
full range (min-max)	26 to 64	26 to 64	
Gender categorical Units: Subjects			
Female	7	7	
Male	6	6	
Diabetes duration Units: year			
median	26	26	
full range (min-max)	17 to 45	17 to 45	
Body mass index Units: kilogram(s)/square metre			
median	27.8	27.8	
full range (min-max)	22.2 to 36.6	22.2 to 36.6	

End points

End points reporting groups

Reporting group title	Dual-hormone --> Single hormone
Reporting group description: Participants went through Dual-hormone and then Single-hormone treatment	
Reporting group title	Single-hormone --> Dual-hormone
Reporting group description: Participants went through single-hormone and then dual-hormone treatment	
Subject analysis set title	DHCL
Subject analysis set type	Intention-to-treat
Subject analysis set description: Data were analyzed in an intention-to-treat approach including periods with any malfunction of the infusion set (e.g. occlusions, kinking of the tube), missing CGM values, and loss of connectivity between study devices to run the closed-loop systems . Repeated-measures ANOVA with a compound symmetry covariance structure was used to test the differences between the two study visits, adjusting for the study order. If data had a skewed distribution, logarithmic transformations were used. If the transformations could not normalize the distribution, nonparametric Wilcoxon signed rank tests were used. Spearman correlations were used to determine relationships. The difference of the time course of PG, insulin and glucagon was tested with a linear mixed model with random effects. A P value of <0.05 was considered statistically significant. Non-predefined outcomes were Bonferroni adjusted for multiple comparisons within each parameter.	
Subject analysis set title	SHCL
Subject analysis set type	Intention-to-treat
Subject analysis set description: Completers of SIngle-hormone	

Primary: Percentage of time in CGM-range below 3.9 mmol/l

End point title	Percentage of time in CGM-range below 3.9 mmol/l
End point description:	
End point type	Primary
End point timeframe: 0-33 hours	

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: percent				
arithmetic mean (standard deviation)	3.7 (± 2.5)	3.9 (± 3.1)		

Statistical analyses

Statistical analysis title	Wilcoxon Signed Rank Test
Comparison groups	DHCL v SHCL

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Wilcoxon (Mann-Whitney)

Primary: Number of carbohydrate interventions to treat hypoglycemia

End point title	Number of carbohydrate interventions to treat hypoglycemia

End point description:

End point type	Primary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: number of rescues	7	12		

Statistical analyses

Statistical analysis title	McNemar
Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Mcnemar

Secondary: Mean glucose

End point title	Mean glucose

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	8.32 (± 1.0)	8.62 (± 1.0)		

Statistical analyses

Statistical analysis title	Mixed Model analysis

Statistical analysis description:

Repeated-measures ANOVA with a compound symmetry covariance structure was used to test the differences between the two study visits, adjusting for the study order. If data had a skewed distribution, logarithmic transformations were used

Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Mixed models analysis

Secondary: Number of events below 3.9 mmol/L

End point title	Number of events below 3.9 mmol/L

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: Numbers of events	29	33		

Statistical analyses

Statistical analysis title	McNemar
Comparison groups	DHCL v SHCL

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Mcnemar

Secondary: Percentage of time in CGM-range between 3.9 and 10 mmol/l

End point title	Percentage of time in CGM-range between 3.9 and 10 mmol/l

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: percent				
arithmetic mean (standard deviation)	66.9 (± 15.1)	64.9 (± 12.1)		

Statistical analyses

Statistical analysis title	Mixed Model analysis

Statistical analysis description:

Repeated-measures ANOVA with a compound symmetry covariance structure was used to test the differences between the two study visits, adjusting for the study order. If data had a skewed distribution, logarithmic transformations were used

Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Mixed models analysis

Secondary: Percentage of time in CGM-range above 10.0 mmol/l

End point title	Percentage of time in CGM-range above 10.0 mmol/l

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: percent				
arithmetic mean (standard deviation)	27.5 (± 14.8)	29.2 (± 10.4)		

Statistical analyses

Statistical analysis title	Mixed Model analysis

Statistical analysis description:

Repeated-measures ANOVA with a compound symmetry covariance structure was used to test the differences between the two study visits, adjusting for the study order. If data had a skewed distribution, logarithmic transformations were used

Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Mixed models analysis

Secondary: Percentage of time in CGM-range below 3.0 mmol/l

End point title	Percentage of time in CGM-range below 3.0 mmol/l

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: percent				
arithmetic mean (standard deviation)	0.6 (± 0.7)	0.6 (± 0.5)		

Statistical analyses

Statistical analysis title	Wilcoxon Signed Rank Test
Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Wilcoxon (Mann-Whitney)

Secondary: Coefficient of variation for sensor glucose

End point title	Coefficient of variation for sensor glucose

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: percent				
arithmetic mean (standard deviation)	39 (± 5)	39 (± 9)		

Statistical analyses

Statistical analysis title	Mixed Model analysis

Statistical analysis description:

Repeated-measures ANOVA with a compound symmetry covariance structure was used to test the differences between the two study visits, adjusting for the study order. If data had a skewed distribution, logarithmic transformations were used

Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Mixed models analysis

Secondary: Mean insulin bolus dose

End point title	Mean insulin bolus dose

End point description:

End point type	Secondary

End point timeframe: 0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: unit(s)				
arithmetic mean (standard deviation)	12.2 (± 6.2)	14.5 (± 5.9)		

Statistical analyses

Statistical analysis title	Mixed Model analysis
Comparison groups	DHCL v SHCL
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Mixed models analysis

Secondary: Mean insulin basal dose

End point title	Mean insulin basal dose
End point description:	
End point type	Secondary
End point timeframe: 0-33 hours	

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: unit(s)				
arithmetic mean (standard deviation)	28.8 (± 9.5)	31.0 (± 8.3)		

Statistical analyses

Statistical analysis title	Mixed Model analysis
Comparison groups	DHCL v SHCL

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Mixed models analysis

Secondary: Mean glucagon dose

End point title	Mean glucagon dose

End point description:

End point type	Secondary

End point timeframe:

0-33 hours

End point values	DHCL	SHCL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	13		
Units: unit(s)				
arithmetic mean (standard deviation)	379 (± 13.8)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were only reported while using the closed-loop systems, e.g. 0-33 hours during each study visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	RedCap
Dictionary version	12.03.02

Reporting groups	
Reporting group title	SHCL: Single-hormone
Reporting group description: -	
Reporting group title	DHCL: Dual-hormone
Reporting group description: -	

Serious adverse events	SHCL: Single-hormone	DHCL: Dual-hormone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	SHCL: Single-hormone	DHCL: Dual-hormone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	12 / 13 (92.31%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	5 / 13 (38.46%)	1 / 13 (7.69%)	
occurrences (all)	5	1	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 13 (30.77%)	5 / 13 (38.46%)	
occurrences (all)	4	5	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hunger			
subjects affected / exposed	13 / 13 (100.00%)	12 / 13 (92.31%)	
occurrences (all)	37	35	
Endocrine disorders			
Nausea			
subjects affected / exposed	4 / 13 (30.77%)	5 / 13 (38.46%)	
occurrences (all)	4	5	

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