Clinical trial results:
PROLOGUES - Prehospital lowering of glucose in Stroke

Summary

EudraCT number	2011-002780-16
Trial protocol	SE
Global end of trial date	31 May 2018

Results information

Result version number	v1 (current)
This version publication date	07 April 2021
First version publication date	07 April 2021

Trial information

Trial identification

Sponsor protocol code	8.4

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	17177, Stockholm, Sweden,
Public contact	David Nathanson, Karolinska Institutet Södersjukhuset, 46 86163449, david.nathanson@sodersjukhuset.se
Scientific contact	David Nathanson, Karolinska Institutet Södersjukhuset, 46 86163449, david.nathanson@sodersjukhuset.se

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 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2018
Global end of trial reached?	Yes
Global end of trial date	31 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to investigate whether Exenatide given in a pre-hospital setting lowers blood glucose levels 4 h after injection, in patients with symptoms of a cerebrovascular lesion.

Protection of trial subjects:

The study was approved by the Central Ethics Committee of Sweden (Ref. No. Ö 62012). Written informed consent was obtained in the ambulance from all participants. Study physician (ML) was on call around the clock for consultations throughout the study period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
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	Sweden: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	7
From 65 to 84 years	9
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was open for inclusion between May 2013 and May 2018 and was stopped due to slow inclusion. The study center was Södersjukhuset in Stockholm, Sweden.

Pre-assignment

Screening details:

Patients transported to hospital by ambulance with symptoms of stroke and hyperglycemia were considered eligible. Inclusion criteria: ≥1 point on the FAST test28 (Face Arm Speech Time), symptoms of stroke with a duration <6 hours, capillary plasma glucose 815 mmol/L, age ≥18 and signed informed consent.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

The control group received standard care for hyperglycemia (ie, insulin treatment at hospital). Patients in the control group received no study treatment in the ambulance. However, no insulin was administrated during the study period as the criterion for insulin treatment was not met for any individual. Patients were kept fasting the first 4 hours to achieve stable and comparable conditions. Venous samples were collected before treatment and after 4 and 24 hours. Capillary glucose measurements were made every hour for the first 4 hours, then every 4 hours until end of study. Total study period was 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Insulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

No insulin was administrated during the study period as the criterion for insulin treatment was not met for any individual.

Arm title	Exenatide

Arm description:

Patients in the exenatide group received a single subcutaneous injection of 10 µg exenatide in the ambulance enroute to hospital. Patients were kept fasting the first 4 hours to achieve stable and comparable conditions. Venous samples were collected before treatment and after 4 and 24 hours. Capillary glucose measurements were made every hour for the first 4 hours, then every 4 hours until end of study. Total study period was 24 hours.

Arm type	Experimental
Investigational medicinal product name	Exenatide
Investigational medicinal product code	SUB21818
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received a single subcutaneous injection of 10 µg exenatide.

Number of subjects in period 1	Control	Exenatide
Started	11	8
Completed	11	8

Baseline characteristics

Reporting groups	
Reporting group title	Control

Reporting group description:

The control group received standard care for hyperglycemia (ie, insulin treatment at hospital). Patients in the control group received no study treatment in the ambulance. However, no insulin was administrated during the study period as the criterion for insulin treatment was not met for any individual. Patients were kept fasting the first 4 hours to achieve stable and comparable conditions. Venous samples were collected before treatment and after 4 and 24 hours. Capillary glucose measurements were made every hour for the first 4 hours, then every 4 hours until end of study. Total study period was 24 hours.

Reporting group title	Exenatide

Reporting group description:

Patients in the exenatide group received a single subcutaneous injection of 10 µg exenatide in the ambulance enroute to hospital. Patients were kept fasting the first 4 hours to achieve stable and comparable conditions. Venous samples were collected before treatment and after 4 and 24 hours. Capillary glucose measurements were made every hour for the first 4 hours, then every 4 hours until end of study. Total study period was 24 hours.

Reporting group values	Control	Exenatide	Total
Number of subjects	11	8	19
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	4	7
From 65-84 years	5	4	9
85 years and over	3	0	3
Age continuous Units: years			
median	80	71	
inter-quartile range (Q1-Q3)	63 to 89	54 to 82	-
Gender categorical Units: Subjects			
Female	5	4	9
Male	6	4	10
Discharge diagnosis Units: Subjects			
Ischemic stroke	9	4	13
Hemorrhagic stroke	0	2	2
Nonstroke	2	2	4
BMI Units: kg/m2			
median	26.4	27.2	
inter-quartile range (Q1-Q3)	23.2 to 31.7	21.6 to 29.5	-

cPglucose			
Units: mmol/L			
median	9.6	9.6	
inter-quartile range (Q1-Q3)	9.0 to 10.8	8.4 to 10.6	-
vPglucose			
Units: mmol/L			
median	9.4	8.8	
inter-quartile range (Q1-Q3)	7.9 to 11.2	6.9 to 10.9	-
Systolic blood pressure			
Units: mm Hg			
median	165	150	
inter-quartile range (Q1-Q3)	130 to 190	124 to 175	-
Diastolic blood pressure			
Units: mm Hg			
median	89	80	
inter-quartile range (Q1-Q3)	80 to 100	76 to 98	-
Heart rate			
Units: Heart rate			
median	88	80	
inter-quartile range (Q1-Q3)	72 to 90	68 to 89	-
NIHSS			
NIHSS, National Institutes of Health Stroke Scale			
Units: Score			
median	1	4.5	
inter-quartile range (Q1-Q3)	0 to 4	1 to 8	-

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
The control group received standard care for hyperglycemia (ie, insulin treatment at hospital). Patients in the control group received no study treatment in the ambulance. However, no insulin was administrated during the study period as the criterion for insulin treatment was not met for any individual. Patients were kept fasting the first 4 hours to achieve stable and comparable conditions. Venous samples were collected before treatment and after 4 and 24 hours. Capillary glucose measurements were made every hour for the first 4 hours, then every 4 hours until end of study. Total study period was 24 hours.	
Reporting group title	Exenatide
Reporting group description:	
Patients in the exenatide group received a single subcutaneous injection of 10 µg exenatide in the ambulance enroute to hospital. Patients were kept fasting the first 4 hours to achieve stable and comparable conditions. Venous samples were collected before treatment and after 4 and 24 hours. Capillary glucose measurements were made every hour for the first 4 hours, then every 4 hours until end of study. Total study period was 24 hours.	

Primary: vPglucose 4 h

End point title	vPglucose 4 h
End point description:	
vPglucose = venous plasma glucose.	
End point type	Primary
End point timeframe:	
4 hours after injection of exenatide.	

End point values	Control	Exenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: mmol/L				
arithmetic mean (standard deviation)	7.0 (± 1.9)	7.6 (± 1.6)		

Statistical analyses

Statistical analysis title	Difference in vPglucose at 4 h
Statistical analysis description:	
Difference in vPglucose at 4 h between control and exenatide.	
Comparison groups	Control v Exenatide

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Wilcoxon (Mann-Whitney)

Primary: cPglucose 4 h

End point title	cPglucose 4 h

End point description:

cPglucose = capillary plasma glucose.

End point type	Primary

End point timeframe:

4 hours after injection of exenatide.

End point values	Control	Exenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: mmol/L				
arithmetic mean (standard deviation)	6.5 (± 1.5)	7.3 (± 2.0)		

Statistical analyses

Statistical analysis title	Difference in cPglucose at 4 h

Statistical analysis description:

Difference in cPglucose at 4 h between control and exenatide.

Comparison groups	Control v Exenatide
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Wilcoxon (Mann-Whitney)

Primary: AUC 04 h

End point title	AUC 04 h

End point description:

End point type	Primary

End point timeframe:

AUC of glucose during the first 4 hours after injection.

End point values	Control	Exenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: glu × h				
arithmetic mean (standard deviation)	32.9 (± 6.2)	33.7 (± 9.6)		

Statistical analyses

Statistical analysis title	Difference AUC 0-4 h
Statistical analysis description: Difference in total glucose exposure measured with AUC.	
Comparison groups	Control v Exenatide
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Wilcoxon (Mann-Whitney)

Primary: AUC 024 h

End point title	AUC 024 h
End point description:	
End point type	Primary
End point timeframe: AUC of glucose during the total study period of 24 hours after injection.	

End point values	Control	Exenatide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: glu × h				
arithmetic mean (standard deviation)	184.3 (± 41)	186.8 (± 40)		

Statistical analyses

Statistical analysis title	Difference AUC 0-24 h
Statistical analysis description: Difference in total glucose exposure measured with AUC.	

Comparison groups	Control v Exenatide
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Total study period, it was 24 hours.	
Adverse event reporting additional description:	
No specific dictionary was used and frequency threshold was not indicated in the protocol. Reporting of adverse events was done continuously for each patient, it was a non-blinded study.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	No specific was used
Dictionary version	n/a

Reporting groups	
Reporting group title	Control
Reporting group description: -	
Reporting group title	Exenatide
Reporting group description: -	

Serious adverse events	Control	Exenatide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Control	Exenatide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	1 / 8 (12.50%)	
Gastrointestinal disorders			
Nausea and vomiting	Additional description: That participant suffered from basilar thrombosis and had vomited before inclusion.		
subjects affected / exposed	0 / 11 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2013	Inclusion of patients with previously known metformintreated type 2 diabetes.
12 March 2014	Widening of glucose inclusion criteria from 1015 mmol/L to 915 mmol/L.
31 May 2016	Widening of glucose inclusion criteria from 915 mmol/L to 815 mmol/L.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The limited sample size warrants some caution in interpretation of the lack of adverse events as a lower frequency than 35% cannot be expected to be detected.33 Another limitation is the short followup of 24 hours.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31518433