Clinical trial results:
A phase 3, randomized, double-blind, parallel trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of hypoglycemia in subjects with type 1 diabetes mellitus (T1DM) compared to placebo and with reference to GlucaGen®

Summary

EudraCT number	2017-002449-31
Trial protocol	DE AT
Global end of trial date	25 May 2018

Results information

Result version number	v1 (current)
This version publication date	29 December 2019
First version publication date	29 December 2019

Trial information

Trial identification

Sponsor protocol code	ZP4207-16137

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03378635
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zealand Pharma A/S
Sponsor organisation address	Sydmarken 11, Søborg, Denmark, 2860
Public contact	Dorte Skydsgaard, Zealand Pharma A/S , +45 5060 3767, dsk@zealandpharma.com
Scientific contact	Dorte Skydsgaard, Zealand Pharma A/S , +45 5060 3767, dsk@zealandpharma.com

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 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2018
Global end of trial reached?	Yes
Global end of trial date	25 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate superiority of dasiglucagon compared to placebo following a single subcutaneous 0.6 mg dose administered to subjects with type 1 diabetes mellitus with insulin-induced hypoglycemia.

Protection of trial subjects:

The trial was conducted in accordance of the World Medical Association Declaration of Helsinki, current guidelines for GCP and local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2017
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	Austria: 68
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	170
EEA total number of subjects	108

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)	164

From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from five trial centers; two in Germany and one each in Austria, Canada and the US.

Pre-assignment

Screening details:

A total of 235 patients were screened of which 170 patients were randomized.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The subjects were randomized 2:1:1 to receive a single fixed SC 0.6 mg dose of dasiglucagon, placebo, or a 1 mg dose of GlucaGen. Since the products were not identical in appearance, unblinded trial personnel were responsible for the handling, preparation and administration of IMP.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dasiglucagon

Arm description: -

Arm type	Experimental
Investigational medicinal product name	dasiglucagon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.6 mg dasiglucagon (0.6 mL).

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of placebo (0.6 mL).

Arm title	GlucaGen

Arm description: -

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

Dosage and administration details:
A single dose of 1mg Glucagen (1mL).

Number of subjects in period 1	Dasiglucagon	Placebo	GlucaGen
Started	84	43	43
Treated	82	43	43
Completed	82	43	43
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Dasiglucagon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	GlucaGen
Reporting group description: -	

Reporting group values	Dasiglucagon	Placebo	GlucaGen
Number of subjects	84	43	43
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	39.2	38.0	40.2
standard deviation	± 12.1	± 13.1	± 11.5
Gender categorical Units: Subjects			
Female	32	16	15
Male	50	27	28
Not recorded	2	0	0
Race Units: Subjects			
White	76	39	39
Other	6	4	4
Not recorded	2	0	0
Weight Units: kilogram(s)			
arithmetic mean	78.3	79.6	80.7
standard deviation	± 13.5	± 13.0	± 15.1
Height Units: centimeter			
arithmetic mean	173.1	174.2	175.9
standard deviation	± 9.44	± 9.15	± 9.71
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	26.1	26.1	25.9
standard deviation	± 4.13	± 3.34	± 3.42
HbA1c Units: percent			
arithmetic mean	7.52	7.17	7.41
standard deviation	± 0.95	± 0.74	± 0.97

Reporting group values	Total		
Number of subjects	170		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female Male Not recorded	63 105 2		
Race Units: Subjects			
White Other Not recorded	154 14 2		
Weight Units: kilogram(s) arithmetic mean standard deviation	- -		
Height Units: centimeter arithmetic mean standard deviation	- -		
Body Mass Index Units: kilogram(s)/square meter arithmetic mean standard deviation	- -		
HbA1c Units: percent arithmetic mean standard deviation	- -		

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomized patients who received at least one dose of trial medication.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All randomized patients who received at least one dose of trial medication.	

Reporting group values	Full Analysis Set	Safety Analysis Set	
Number of subjects	168	168	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	39.1	39.1	
standard deviation	± 12.2	± 12.2	
Gender categorical Units: Subjects			
Female	63	63	
Male	105	105	
Not recorded			
Race Units: Subjects			
White	154	154	
Other	14	14	
Not recorded			
Weight Units: kilogram(s)			
arithmetic mean	79.2	79.2	
standard deviation	± 13.7	± 13.7	
Height Units: centimeter			
arithmetic mean	174.1	174.1	
standard deviation	± 9.45	± 9.45	
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	26.1	26.1	
standard deviation	± 3.75	± 3.75	
HbA1c Units: percent			
arithmetic mean	7.40	7.40	
standard deviation	± 0.91	± 0.91	

End points

End points reporting groups

Reporting group title	Dasiglucagon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	GlucaGen
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized patients who received at least one dose of trial medication.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who received at least one dose of trial medication.	

Primary: Time to plasma glucose recovery

End point title	Time to plasma glucose recovery
End point description:	
plasma glucose recovery was defined as first increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline without administration of rescue IV glucose. If recovery had not occurred at 45 minutes after investigational product injection, censoring was applied irrespective of the use of rescue IV glucose.	
End point type	Primary
End point timeframe:	
Time from administration/baseline	

End point values	Dasiglucagon	Placebo	GlucaGen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	43	43	
Units: minutes				
median (confidence interval 95%)	10 (10 to 10)	40 (30 to 40)	12 (10 to 12)	

Statistical analyses

Statistical analysis title	log-rank test: Dasiglucagon versus placebo
Statistical analysis description:	
The treatment group difference between dasiglucagon and placebo was evaluated inferentially using a pairwise two-sided log rank test.	
Comparison groups	Placebo v Dasiglucagon

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Plasma glucose recovery at defined times

End point title	Plasma glucose recovery at defined times

End point description:

End point type	Secondary

End point timeframe:

time from administration/baseline

End point values	Dasiglucagon	Placebo	GlucaGen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	43	43	
Units: subjects				
Glucose recovery at 30 minutes	82	20	43	
Glucose recovery at 20 minutes	81	6	42	
Glucose recovery at 15 minutes	81	1	41	
Glucose recovery at 10 minutes	53	0	21	

Statistical analyses

Statistical analysis title	Fisher's Exact test: Dasiglucagon versus placebo

Statistical analysis description:

Pairwise test of independent binomial proportions with Fisher's Exact test comparing Dasiglucagon versus Placebo. Testing followed an a priori defined hierarchical inferential test order, proceeding until the first failure to reject the null hypothesis comparing Dasiglucagon versus Placebo.

Comparison groups	Dasiglucagon v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Fisher exact

Notes:

[1] - p-value was <0.001 at all time points (10, 15, 20 and 30 minutes)

Secondary: Plasma Glucose Change from Baseline

End point title	Plasma Glucose Change from Baseline

End point description:

End point type	Secondary

End point timeframe:

Time from administration/baseline

End point values	Dasiglucagon	Placebo	GlucaGen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	43	43	
Units: mg/dL				
arithmetic mean (standard deviation)				
At 30 minutes	90.9 (± 18.2)	19.1 (± 13.0)	88.5 (± 19.2)	
At 20 minutes	59.7 (± 15.0)	8.7 (± 10.8)	58.4 (± 15.6)	
At 15 minutes	43.5 (± 12.51)	6.65 (± 6.82)	44.1 (± 14.0)	
At 10 minutes	23.9 (± 9.84)	-0.14 (± 5.65)	22.0 (± 10.0)	

Statistical analyses

Statistical analysis title	Least squares means: Dasiglucagon versus Placebo

Statistical analysis description:

This key secondary endpoint was analyzed with the plasma glucose change from baseline at rescue carried forward in those patients who required rescue IV glucose before plasma glucose ≥20 mg/dL recovery. Each of these change from baseline variables was analyzed using an ANCOVA model, with treatment group modeled as a fixed effect and with the baseline plasma glucose modeled as a covariate. The group difference was evaluated inferentially until the first failure to reject, starting at 30 minutes.

Comparison groups	Dasiglucagon v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	ANCOVA

Notes:

[2] - The p-value was <0.001 at all time points (10, 15, 20 and 30 minutes).

Secondary: Time to First Plasma Glucose Concentration ≥70 mg/dL

End point title	Time to First Plasma Glucose Concentration ≥70 mg/dL

End point description:

Time to first plasma glucose concentration ≥70 mg/dL (3.9 mmol/L) without administration of rescue IV glucose. If the ≥70 mg/dL endpoint was not met within 45 minutes post-dosing, the time of the last valid plasma glucose measurement up to 45 minutes was the censoring time.

End point type	Secondary

End point timeframe:

Time from administration/baseline

End point values	Dasiglucagon	Placebo	GlucaGen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	43	43	
Units: minute				
median (confidence interval 95%)	8 (8 to 8)	25 (20 to 30)	8 (8 to 10)	

Statistical analyses

Statistical analysis title	Least squares means: Dasiglucagon versus Placebo

Statistical analysis description:

The treatment group difference between dasiglucagon and placebo was evaluated using a Kaplan-Meier estimate with 95% CI, p-value based on a pairwise two-sided log-rank test versus placebo.

Comparison groups	Dasiglucagon v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Pharmacodynamics - Area under the effect curve (0-30 minutes)

End point title	Pharmacodynamics - Area under the effect curve (0-30 minutes)

End point description:

End point type	Secondary

End point timeframe:

Time from administration/baseline

End point values	Dasiglucagon	Placebo	GlucaGen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	43	43	
Units: mg.h/dL				
arithmetic mean (standard deviation)	21.0 (± 5.26)	3.57 (± 2.86)	20.4 (± 5.49)	

Statistical analyses

Statistical analysis title	Least squares means: Dasiglucagon versus Placebo

Statistical analysis description:

The log-transformed AUC endpoint is analyzed using an ANCOVA model with treatment as fixed effect and baseline plasma glucose modeled as a covariate. The least squares means treatment group differences will be back-transformed (anti-logged) for presentation as a ratio of the treatment group geometric means, with their corresponding 95% CI.

Comparison groups	Dasiglucagon v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.171

Secondary: Pharmacokinetics - Area under the plasma concentration curve (0-90 minutes)

End point title	Pharmacokinetics - Area under the plasma concentration curve (0-90 minutes)[3]

End point description:

The area under the concentration-time curve from zero up to the concentration at 90 minutes. To calculate AUC the standard trapezoidal method was used, based on actual rather than nominal time points.

End point type	Secondary

End point timeframe:

0-90 minutes

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No results are presented for the placebo group, as no drug was given in this group.

End point values	Dasiglucagon	GlucaGen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	43		
Units: pmol.h/L				
arithmetic mean (standard deviation)	1520 (± 518)	1350 (± 372)		

Statistical analyses

Statistical analysis title	Least squares mean

Statistical analysis description:

LSM ratio for glucagon:dasiglucagon

Comparison groups	Dasiglucagon v GlucaGen

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.144
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.801
upper limit	1.033

Secondary: Pharmacokinetics - Area under the plasma concentration curve 0-120 minutes

End point title	Pharmacokinetics - Area under the plasma concentration curve 0-120 minutes[4]

End point description:

The area under the concentration-time curve from zero up to the concentration at 120 minutes. To calculate AUC the standard trapezoidal method was used, based on actual rather than nominal time points.

End point type	Secondary

End point timeframe:

0-120 minutes

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No results are presented for the placebo group, as no drug was given in this group.

End point values	Dasiglucagon	GlucaGen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	43		
Units: pmol.h/L				
arithmetic mean (standard deviation)	1860 (± 580)	1550 (± 422)		

Statistical analyses

Statistical analysis title	Least squares mean

Statistical analysis description:

LSM ratio for glucagon:dasiglucagon

Comparison groups	Dasiglucagon v GlucaGen
Number of subjects included in analysis	125
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	least squares mean
Point estimate	0.844

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.749
upper limit	0.951

Secondary: Pharmacokinetics - Maximum concentration

End point title	Pharmacokinetics - Maximum concentration[5]

End point description:

End point type	Secondary

End point timeframe:

0-120 minutes

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No results are presented for the placebo group, as no drug was given in this group.

End point values	Dasiglucagon	GlucaGen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	43		
Units: pmol/L				
arithmetic mean (standard deviation)	1380 (± 519)	1570 (± 542)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - Time to maximum concentration

End point title	Pharmacokinetics - Time to maximum concentration[6]

End point description:

The actual sampling time recorded for the maximum concentration.

End point type	Secondary

End point timeframe:

0-120 minutes

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No results are presented for the placebo group, as no drug was given in this group.

End point values	Dasiglucagon	GlucaGen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	43		
Units: hour				
arithmetic mean (standard deviation)	0.669 (± 0.158)	0.312 (± 0.117)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the first trial-related activity after the patient has signed the informed consent to the end of the follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Dasiglucagon
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	GlucaGen

Reporting group description: -

Serious adverse events	Dasiglucagon	Placebo	GlucaGen
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	0 / 43 (0.00%)	0 / 43 (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: 5 %

Non-serious adverse events	Dasiglucagon	Placebo	GlucaGen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 82 (80.49%)	14 / 43 (32.56%)	32 / 43 (74.42%)
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 82 (12.20%)	2 / 43 (4.65%)	5 / 43 (11.63%)
occurrences (all)	10	2	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	45 / 82 (54.88%)	1 / 43 (2.33%)	23 / 43 (53.49%)
occurrences (all)	46	1	24
Vomiting			

subjects affected / exposed	19 / 82 (23.17%)	1 / 43 (2.33%)	9 / 43 (20.93%)
occurrences (all)	25	1	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 82 (6.10%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	5	1	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	23 / 82 (28.05%)	5 / 43 (11.63%)	9 / 43 (20.93%)
occurrences (all)	39	6	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2018	The following key changes and clarifications to the protocol were made: - Coagulation was removed as a laboratory safety endpoint. - The need for using additional contraception for patients using systemic contraceptives was removed for the inclusion criteria. - Local German requirements were added: o Insulin glulisine (Apidra®) was defined as an investigational product. o The Investigator was to address the causality to dasiglucagon/placebo/GlucaGen® and to insulin glulisine®, respectively. o The AE summary for AEs related to insulin glulisine (Apidra®) was to be presented as an appendix to the clinical trial report. - C-peptide and coagulation were added as parameters collected from samples at the Screening visit. - Alterations were made for determining sample size. - Clarification was added for patient withdrawals and missing data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported