Clinical trial results:
A phase 3, Randomized, Double-Blind, Parallel Group Safety Trial to Evaluate the Immunogenicity of Dasiglucagon And GlucaGen® Administered Subcutaneously in patients with Type 1 Diabetes Mellitus (T1DM)

Summary

EudraCT number	2017-000062-30
Trial protocol	DE AT
Global end of trial date	13 February 2018

Results information

Result version number	v1 (current)
This version publication date	28 February 2019
First version publication date	28 February 2019

Trial information

Trial identification

Sponsor protocol code	ZP4207-16136

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03216226
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 127866

Notes:

Sponsors

Sponsor organisation name	Zealand Pharma A/S
Sponsor organisation address	Smedeland 26, Glostrup, Denmark, 2600
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	22 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2018
Global end of trial reached?	Yes
Global end of trial date	13 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the immunogenicity of repeated single doses of dasiglucagon and GlucaGen following subcutaneous (s.c.) administration in T1DM patients.

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	15 March 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: 31
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Canada: 54
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	112
EEA total number of subjects	48

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)	108
From 65 to 84 years	4

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from 7 trial centers in Austria (1 center), Canada (3 centers), Germany (1 center) and the USA (2 centers) between 28 June 2017 (first patient enrolled) and 13 February 2018 (last patient completed trial).

Pre-assignment

Screening details:

A total of 131 patients were screened of which 19 patients were not 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:

Patients with T1DM were randomly assigned in a 1:1 ratio to receive 3 SC injections of either dasiglucagon (0.6 mg) or GlucaGen® (1 mg), with 1 week between doses. 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:

Three doses of 0.6 mg dasiglucagon (0.6 mL) given at weekly intervals.

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:

Three doses of 1mg Glucagen (1mL) given at weekly intervals.

Number of subjects in period 1	Dasiglucagon	GlucaGen
Started	57	55
Treated	57	54
Completed	52	50
Not completed	5	5
Adverse event, non-fatal	3	-
Missed injection visit	1	1
Withdrawn: veins unsuitable for blood draw	-	1
Protocol deviation	1	3

Baseline characteristics

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

Reporting group values	Dasiglucagon	GlucaGen	Total
Number of subjects	57	55	112
Age categorical Units: Subjects			
Adults (18-64 years)	55	53	108
From 65-84 years	2	2	4
Age continuous Units: years			
arithmetic mean	45.3	38.8	
standard deviation	± 12.21	± 13.65	-
Gender categorical Units: Subjects			
Female	16	23	39
Male	41	32	73
Race Units: Subjects			
White	50	53	103
Other	7	2	9
Height Units: centimetres			
arithmetic mean	174.1	173.6	
standard deviation	± 9.54	± 7.65	-
Weight Units: kilogram(s)			
arithmetic mean	82.9	82.7	
standard deviation	± 18.44	± 16.25	-
BMI Units: kilogram(s)/square meter			
arithmetic mean	27.2	27.4	
standard deviation	± 4.88	± 4.70	-

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: All patients of the safety analysis set with at least 1 measurement of ADA titer at baseline	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who were randomly assigned and received at least 1 dose of IMP	

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	111	111	
Age categorical Units: Subjects			
Adults (18-64 years)	107	107	
From 65-84 years	4	4	
Age continuous Units: years			
arithmetic mean	42.1	42.1	
standard deviation	± 13.29	± 13.29	
Gender categorical Units: Subjects			
Female	38	38	
Male	73	73	
Race Units: Subjects			
White	102	102	
Other	9	9	
Height Units: centimetres			
arithmetic mean	173.9	173.9	
standard deviation	± 8.64	± 8.64	
Weight Units: kilogram(s)			
arithmetic mean	82.8	82.8	
standard deviation	± 17.33	± 17.33	
BMI Units: kilogram(s)/square meter			
arithmetic mean	27.3	27.3	
standard deviation	± 4.77	± 4.77	

End points

End points reporting groups

Reporting group title	Dasiglucagon
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 patients of the safety analysis set with at least 1 measurement of ADA titer at baseline	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who were randomly assigned and received at least 1 dose of IMP	

Primary: Overall ADA

End point title	Overall ADA[1]

End point description:

For calculating the overall ADA incidence, patient numbers from both groups were summed and then divided by the number of evaluable patients. Baseline-positive patients without any samples available after IMP administration were excluded.

Numbers and percentages of incidences in each treatment group and the incidence difference between dasiglucagon and GlucaGen® with its 95% exact confidence limits were planned to be provided but were not generated because no ADA-positive patients occurred in the trial.

End point type	Primary

End point timeframe:

From baseline to end of trial

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were planned but were not generated because no ADA-positive patients occurred in the trial.

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: Subjects				
Yes	0	0	0	
No	56	54	110	
Missing	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-induced ADA

End point title	Treatment-induced ADA

End point description:

End point type	Secondary

End point timeframe:

From baseline to end of trial

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: subjects				
Yes	0	0	0	
No	56	54	110	
Missing	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-boosted ADA

End point title	Treatment-boosted ADA

End point description:

End point type	Secondary

End point timeframe:

From baseline to end of trial

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: subjects				
Yes	0	0	0	
No	56	54	110	
Missing	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and titer of neutralizing activity of ADA-positive patients

End point title	Incidence and titer of neutralizing activity of ADA-positive

	patients

End point description:

This secondary immunogenicity endpoint was not analyzed since there were no overall ADA incidents in the trial population.

End point type	Secondary

End point timeframe:

From baseline to end of trial

End point values	Dasiglucagon	GlucaGen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - Area under the plasma concentration curve (0-30 minutes)

End point title	Pharmacokinetics - Area under the plasma concentration curve (0-30 minutes)

End point description:

The area under the concentration-time curve from zero up to the concentration at 30 minutes. To calculate AUC the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

End point type	Secondary

End point timeframe:

0-30 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: pmol.h/L				
arithmetic mean (standard deviation)				
Visit 2	425 (± 220)	548 (± 226)	485 (± 230)	
Visit 4	499 (± 371)	546 (± 181)	522 (± 294)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The area under the concentration-time curve from zero up to the concentration at 90 minutes. To calculate AUC the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

End point type	Secondary

End point timeframe:

0-90 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: pmol.h/L				
arithmetic mean (standard deviation)				
Visit 2	1560 (± 615)	1290 (± 434)	1430 (± 549)	
Visit 4	1640 (± 611)	1290 (± 379)	1470 (± 540)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - Maximum concentration

End point title	Pharmacokinetics - Maximum concentration

End point description:

The measured maximum plasma concentration after administration at Visit 2 and Visit 4

End point type	Secondary

End point timeframe:

0-120 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: pmol/L				
arithmetic mean (standard deviation)				
Visit 2	1390 (± 609)	1490 (± 537)	1440 (± 574)	
Visit 4	1820 (± 2460)	1430 (± 498)	1630 (± 1790)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - Time to maximum concentration

End point title	Pharmacokinetics - Time to maximum concentration

End point description:

The actual sampling time recorded for the maximum concentration.

End point type	Secondary

End point timeframe:

0-120 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: hours				
median (full range (min-max))				
Visit 2	0.5 (0.167 to 1.5)	0.483 (0.0833 to 0.55)	0.5 (0.0833 to 1.5)	
Visit 4	0.5 (0.0833 to 1.5)	0.5 (0.0833 to 0.517)	0.5 (0.0833 to 1.5)	

Statistical analyses

No statistical analyses for this end point

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:

The area under the baseline-adjusted effect curve from zero up to the concentration measured at 30 minutes. To calculate AUE the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

End point type	Secondary

End point timeframe:

0-30 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: mmol.h/L				
arithmetic mean (standard deviation)				
Visit 2	0.799 (± 0.449)	0.886 (± 0.504)	0.841 (± 0.476)	

Visit 4	0.869 (± 0.375)	0.895 (± 0.511)	0.881 (± 0.443)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics - Area under the effect curve (0-90 minutes)

End point title	Pharmacodynamics - Area under the effect curve (0-90 minutes)

End point description:

The area under the baseline-adjusted effect curve from zero up to the concentration measured at 90 minutes. To calculate AUE the linear trapezoidal rule was used for the ascending part and the logarithmic trapezoidal rule was used for the descending part.

End point type	Secondary

End point timeframe:

0-90 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: mmol.h/L				
arithmetic mean (standard deviation)				
Visit 2	5.9 (± 2.42)	5.86 (± 3.14)	5.88 (± 2.78)	
Visit 4	6.47 (± 2.28)	6.04 (± 2.63)	6.26 (± 2.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics - CEmax

End point title	Pharmacodynamics - CEmax

End point description:

Change from baseline plasma glucose to maximum plasma glucose measured after dosing.

End point type	Secondary

End point timeframe:

0-120 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: mmol/L				
arithmetic mean (standard deviation)				
Visit 2	6.25 (± 2.5)	6 (± 3.01)	6.12 (± 2.75)	
Visit 4	6.88 (± 2.43)	6.21 (± 2.65)	6.55 (± 2.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics - TEmax

End point title	Pharmacodynamics - TEmax

End point description:

The time to reach the maximum change from baseline in plasma glucose measured after dosing.

End point type	Secondary

End point timeframe:

0-120 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: hours				
median (full range (min-max))				
Visit 2	1.5 (0.0833 to 1.57)	1.5 (0.483 to 1.6)	1.5 (0.0833 to 1.6)	
Visit 4	1.5 (0.167 to 1.58)	1.5 (0.0833 to 1.52)	1.5 (0.0833 to 1.58)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics - An increase in the plasma glucose concentration of ≥20 mg/dL within 30 minutes after treatment - Visit 2

End point title	Pharmacodynamics - An increase in the plasma glucose concentration of ≥20 mg/dL within 30 minutes after treatment - Visit 2

End point description:

End point type	Secondary

End point timeframe:

0-30 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	57	54	111	
Units: subjects				
Yes	54	51	105	
No	3	3	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics - An increase in the plasma glucose concentration of ≥20 mg/dL within 30 minutes after treatment - Visit 4

End point title	Pharmacodynamics - An increase in the plasma glucose concentration of ≥20 mg/dL within 30 minutes after treatment - Visit 4

End point description:

End point type	Secondary

End point timeframe:

0-30 minutes

End point values	Dasiglucagon	GlucaGen	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	49	101	
Units: subjects				
Yes	51	47	98	
No	1	2	3	

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	20.0

Reporting groups

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

Reporting group description: -

Serious adverse events	Dasiglucagon	GlucaGen	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dasiglucagon	GlucaGen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 57 (73.68%)	43 / 54 (79.63%)	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 57 (14.04%)	3 / 54 (5.56%)	
occurrences (all)	14	4	
Dizziness			
subjects affected / exposed	2 / 57 (3.51%)	3 / 54 (5.56%)	
occurrences (all)	2	3	

Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	2 / 57 (3.51%)	4 / 54 (7.41%)	
occurrences (all)	2	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	26 / 57 (45.61%)	23 / 54 (42.59%)	
occurrences (all)	43	33	
Vomiting			
subjects affected / exposed	12 / 57 (21.05%)	8 / 54 (14.81%)	
occurrences (all)	18	9	
Diarrhoea			
subjects affected / exposed	4 / 57 (7.02%)	2 / 54 (3.70%)	
occurrences (all)	4	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 57 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	4	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 57 (10.53%)	8 / 54 (14.81%)	
occurrences (all)	7	9	
Upper respiratory tract infection			
subjects affected / exposed	2 / 57 (3.51%)	4 / 54 (7.41%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	28 / 57 (49.12%)	29 / 54 (53.70%)	
occurrences (all)	581	447	
Hyperglycaemia			
subjects affected / exposed	3 / 57 (5.26%)	2 / 54 (3.70%)	
occurrences (all)	3	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2017	In this substantial amendment, the following changes were made to the original protocol to revise details of the safety assessment of patients and correct changes, errors or inconsistencies in the description of the operational set up of the trial: • Clarification on the statistical method and anti-drug antibody (ADA) assays • Update of exclusion criterion on blood pressure • Update of exclusion criterion on alcohol/drug abuse • Specification of prohibited concomitant medication • Additional ECG assessment added • Clinical event of interest added • Treatment options for patients experiencing hypo- or hyperglycemia prior dosing • Monitoring of patients' electrolyte levels • Monitoring of potential pregnancies • Additional visits required for patients discontinuing treatment prematurely • Specification on time windows for assessments • Specification of the requirements at the dosing visits • Responsibility of unblinded trial personnel • Randomization of replacement patients • Clarification to the reporting of (Serious) Adverse Events • Clarification on case report forms • Subgroup analysis added to the statistical section • Administrative changes
21 August 2017	This substantial amendment was prepared in order to investigate how pharmacodynamic and pharmacokinetic endpoints correlate with potential anti-drug antibody responses that may develop. In order to investigate this in patients that may develop antibodies late during the course of the trial, an extra visit was to be implemented for patients, who developed anti-drug antibodies after trial drug administration. The amendment also included an additional pharmacodynamic endpoint and specified that patients who discontinue the trial prematurely were not to be replaced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported