Clinical trial results:
A phase 3, randomized, double-blind, placebo- and active-controlled, parallel-arm trial to assess the efficacy, safety, and pharmacokinetics of dasiglucagon relative to placebo and GlucaGen® when administered as a rescue therapy for severe hypoglycemia in children with T1DM treated with insulin

Summary

EudraCT number	2018-000892-33
Trial protocol	DE SI
Global end of trial date	28 June 2019

Results information

Result version number	v1 (current)
This version publication date	04 April 2020
First version publication date	04 April 2020

Trial information

Trial identification

Sponsor protocol code	ZP4207-17086

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03667053
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	Ramin Tehranchi, Zealand Pharma A/S, +45 5060 3793, rte@zealandpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002233-PIP01-17
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	17 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2019
Global end of trial reached?	Yes
Global end of trial date	28 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that dasiglucagon is superior to placebo following a single injection of 0.6 mg of dasiglucagon in treating hypoglycemia in children with type 1 diabetes mellitus (T1DM).

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	28 September 2018
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	Slovenia: 11
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	42
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)	16
Adolescents (12-17 years)	26
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from five trial centers; 3 in the US and one each in Slovenia and Germany.

Pre-assignment

Screening details:

A total of 59 patients were screened of which 42 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 and stratified by age intervals: 6 to <12 years, and 12 to <18 years to receive dasiglucagon, placebo, or GlucaGen.
In Germany a staggered approach was used. A positive safety assessment was needed for at least 10 patients in the older age group (overall) before younger patients were allowed to be enrolled.
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). A half dose was recommended for children below 25kg.

Number of subjects in period 1	Dasiglucagon	Placebo	GlucaGen
Started	21	11	10
Treated	20	11	10
Completed	20	11	10
Not completed	1	0	0
Consent withdrawn by subject	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	21	11	10
Age categorical Units: Subjects			
Children (2-11 years)	8	4	4
Adolescents (12-17 years)	13	7	6
Age continuous Units: years			
arithmetic mean	12.3	12.8	12.4
standard deviation	± 3.42	± 3.25	± 3.50
Gender categorical Units: Subjects			
Female	10	6	2
Male	11	5	8
Race Units: Subjects			
White	20	10	10
Other	1	0	0
Missing	0	1	0
Height Units: centimeter(s)			
arithmetic mean	154.6	161.1	158.5
standard deviation	± 18.32	± 19.45	± 20.10
Weight Units: kilogram(s)			
arithmetic mean	51.54	54.95	48.81
standard deviation	± 22.202	± 21.404	± 14.992
BMI Units: kilogram(s)/square meter			
arithmetic mean	20.74	20.39	18.92
standard deviation	± 6.057	± 4.885	± 2.617

Reporting group values	Total		
Number of subjects	42		
Age categorical Units: Subjects			
Children (2-11 years)	16		
Adolescents (12-17 years)	26		

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female Male	18 24		
Race Units: Subjects			
White Other Missing	40 1 1		
Height Units: centimeter(s) arithmetic mean standard deviation	- -		
Weight Units: kilogram(s) arithmetic mean standard deviation	- -		
BMI Units: kilogram(s)/square meter 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 patients of the safety analysis set. Treatment assignment was based on the randomized treatment. Assignment to the stratification factor injection site was based on the planned and not the actual used injection site.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who were randomized and received at least 1 dose of IMP. Treatment assignment was based on the treatment actually received.

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	41	41	
Age categorical Units: Subjects			
Children (2-11 years) Adolescents (12-17 years)	16 25	16 25	
Age continuous Units: years arithmetic mean standard deviation	 12.5 ± 3.32	 12.5 ± 3.32	

Gender categorical Units: Subjects			
Female	18	18	
Male	23	23	
Race Units: Subjects			
White	39	39	
Other	1	1	
Missing	1	1	
Height Units: centimeter(s)			
arithmetic mean	157.3	157.3	
standard deviation	± 18.78	± 18.78	
Weight Units: kilogram(s)			
arithmetic mean	51.79	51.79	
standard deviation	± 20.106	± 20.106	
BMI Units: kilogram(s)/square meter			
arithmetic mean	20.20	20.20	
standard deviation	± 5.050	± 5.050	

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 patients of the safety analysis set. Treatment assignment was based on the randomized treatment. Assignment to the stratification factor injection site was based on the planned and not the actual used injection site.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who were randomized and received at least 1 dose of IMP. Treatment assignment was based on the treatment actually received.	

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. Patients who received rescue IV glucose before 45 minutes and patients not recovering within 45 minutes after dosing were censored at 45 minutes.	
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	20	11[1]	10	
Units: minute				
median (confidence interval 95%)	10.00 (8.00 to 12.00)	30.00 (20.00 to 45)	10.00 (8.00 to 12.00)	

Notes:

[1] - Upper CL for placebo median is set to 45 minutes (censored value)

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	Dasiglucagon v Placebo

Number of subjects included in analysis	31
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:

The number of subjects achieving a ≥20 mg/dL (1.1 mmol/L) increase in plasma glucose from baseline within the specified 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	20	11	10	
Units: subjects				
Glucose recovery at 30 minutes	20	6	10	
Glucose recovery at 20 minutes	20	2	10	
Glucose recovery at 15 minutes	19	0	10	
Glucose recovery at 10 minutes	13	0	6	

Statistical analyses

Statistical analysis title	Recovery rates of dasiglucagon and placebo

Statistical analysis description:

The recovery rates of dasiglucagon and placebo were compared at each time point using a Cochran-Mantel-Haenszel test stratified by age group and injection site.

Comparison groups	Dasiglucagon v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - p-value = 0.0005 at 10 minutes
p-value was <0.0001 at 15 and 20 minutes
p-value = 0.0073 at 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	20	11	10	
Units: mg/dL				
arithmetic mean (standard deviation)				
At 30 minutes	98.459 (± 19.6527)	17.510 (± 15.6313)	85.225 (± 12.5052)	
At 20 minutes	65.369 (± 15.2461)	7.322 (± 13.3543)	58.000 (± 10.5297)	
At 15 minutes	45.342 (± 15.0860)	0.835 (± 11.1276)	40.631 (± 9.7317)	
At 10 minutes	27.225 (± 13.6768)	-3.405 (± 8.0276)	20.919 (± 6.7227)	

Statistical analyses

Statistical analysis title	Least squares means: Dasiglucagon versus Placebo

Statistical analysis description:

Change from baseline in plasma glucose at 30, 20, 15, and 10 minutes after IMP injection was calculated using nominal sampling times and analyzed using an analysis of variance model with treatment, age group and injection site for each endpoint.

Comparison groups	Dasiglucagon v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANOVA

Notes:

[3] - The p-value was <0.0001 at all time points (10, 15, 20 and 30 minutes)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Age group 6-11 years - Dasiglucagon
Reporting group description: -	
Reporting group title	Age group 6-11 years - Placebo
Reporting group description: -	
Reporting group title	Age group 6-11 years - GlucaGen
Reporting group description: -	
Reporting group title	Age group 12-17 years - Dasiglucagon
Reporting group description: -	
Reporting group title	Age group 12-17 years - Placebo
Reporting group description: -	
Reporting group title	Age group 12-17 years - Glucagen

Reporting group description: -

Serious adverse events	Age group 6-11 years - Dasiglucagon	Age group 6-11 years - Placebo	Age group 6-11 years - GlucaGen
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Age group 12-17 years - Dasiglucagon	Age group 12-17 years - Placebo	Age group 12-17 years - Glucagen
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	0 / 6 (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	Age group 6-11 years - Dasiglucagon	Age group 6-11 years - Placebo	Age group 6-11 years - GlucaGen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	1 / 4 (25.00%)	4 / 4 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injection site oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injection site induration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infusion site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infusion site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	2	0	2
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Age group 12-17 years - Dasiglucagon	Age group 12-17 years - Placebo	Age group 12-17 years - Glucagen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	6 / 7 (85.71%)	5 / 6 (83.33%)
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Injection site oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injection site induration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infusion site bruising			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infusion site pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	11 / 12 (91.67%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	12	0	1
Vomiting			
subjects affected / exposed	8 / 12 (66.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	11	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 7 (57.14%)	2 / 6 (33.33%)
occurrences (all)	1	16	2

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