Clinical trial results:
A phase 3b, randomized, double-blind, crossover trial to compare the efficacy and safety of 2 different batches of subcutaneous dasiglucagon in patients with type 1 diabetes mellitus

Summary

EudraCT number	2018-003834-34
Trial protocol	AT
Global end of trial date	30 July 2019

Results information

Result version number	v1 (current)
This version publication date	23 August 2020
First version publication date	23 August 2020

Trial information

Trial identification

Sponsor protocol code	ZP4207-17084

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03895697
WHO universal trial number (UTN)	-
Other trial identifiers	IND #: 127866

Notes:

Sponsors

Sponsor organisation name	Zealand Pharma A/S
Sponsor organisation address	Sydmarken 11, Søborg, Denmark, 2860
Public contact	Stine Just Maarbjerg, Zealand Pharma A/S, +45 5060 3846, SMaarbjerg@zealandpharma.com
Scientific contact	Ramin Tehranchi, Zealand Pharma A/S, +45 5060 3793, RTehranchi@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	17 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2019
Global end of trial reached?	Yes
Global end of trial date	30 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to show non-inferiority of the efficacy of a single subcutaneous dose of dasiglucagon batch B relative to that of dasiglucagon batch A for treatment of hypoglycemia in patients with type 1 diabetes mellitus

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	10 March 2019
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: 25
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Canada: 21
Worldwide total number of subjects	92
EEA total number of subjects	71

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)	92
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from 4 trial centers in Austria (1 center), Canada (1 center) and Germany (2 centers) between 10 March 2019 (first patient enrolled) and 30 July 2019 (Last patient completed trial)

Pre-assignment

Screening details:

A total of 109 patients were screened of which 17 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:

In order to avoid bias in patient selection and in the evaluation of clinical assessments, patients were randomly assigned 1:1 to either dasiglucagon Batch A or dasiglucagon Batch B as their initial dose and the other as the second dose.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dasiglucagon Batch A crossover to Dasiglucagon Batch B

Arm description:

Single treatment with Dasiglucagon Batch A followed by cross-over to a single treatment with Dasiglucagon Batch B.

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:

One dose of 0.6 mg dasiglucagon

Arm title	Dasiglucagon Batch B crossover to Dasiglucagon Batch A

Arm description:

Single treatment with Dasiglucagon Batch B followed by cross-over to a single treatment with Dasiglucagon Batch A.

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:

One dose of 0.6 mg dasiglucagon

Number of subjects in period 1	Dasiglucagon Batch A crossover to Dasiglucagon Batch B	Dasiglucagon Batch B crossover to Dasiglucagon Batch A
Started	46	46
Treated	45	45
Completed	42	41
Not completed	4	5
Consent withdrawn by subject	-	1
Unable to come for re-scheduled dosing visit	1	-
Didn't want to participate in hypo induction	2	1
Adverse event, non-fatal	-	2
Limited availability	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Dasiglucagon Batch A crossover to Dasiglucagon Batch B
Reporting group description:	
Single treatment with Dasiglucagon Batch A followed by cross-over to a single treatment with Dasiglucagon Batch B.	
Reporting group title	Dasiglucagon Batch B crossover to Dasiglucagon Batch A
Reporting group description:	
Single treatment with Dasiglucagon Batch B followed by cross-over to a single treatment with Dasiglucagon Batch A.	

Reporting group values	Dasiglucagon Batch A crossover to Dasiglucagon Batch B	Dasiglucagon Batch B crossover to Dasiglucagon Batch A	Total
Number of subjects	46	46	92
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	36.7	36.3	
standard deviation	± 11.75	± 12.07	-
Gender categorical			
Units: Subjects			
Female	18	20	38
Male	28	26	54
Race			
Units: Subjects			
White	44	46	90
Other	2	0	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	45	46	91
Body mass index class			
Units: Subjects			
< 25 kg/m^2	20	21	41
25-<30 kg/m^2	22	20	42
30-<35 kg/m^2	3	3	6
>=35 kg/m^2	1	2	3
Height			
Units: centimeter(s)			
arithmetic mean	175.7	175.1	
standard deviation	± 9.47	± 10.80	-
Weight			
Units: kilogram(s)			
arithmetic mean	80.17	80.96	
standard deviation	± 14.662	± 17.883	-

Body mass index Units: kilogram(s)/square meter			
arithmetic mean	25.82	26.18	
standard deviation	± 3.301	± 4.033	-
Time since detection of diabetes Units: years			
arithmetic mean	19.27	18.44	
standard deviation	± 10.497	± 11.232	-

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomly assigned patients who had received at least 1 dose of IMP.

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

Subject analysis set description:

All randomly assigned patients who had received at least 1 dose of IMP.

Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of full analysis set who had received both treatments and had efficacy data available to evaluate the primary endpoint for both treatments. Patients could be excluded if relevant protocol deviations were documented (e.g. the use of prespecified concomitant medications).

Subject analysis set title	Dasiglucagon Batch A (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of per protocol analysis set that received Batch A in either arm.

Subject analysis set title	Dasiglucagon Batch B (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of per protocol analysis set that received Batch B in either arm.

Reporting group values	Full analysis set	Safety analysis set	Per protocol analysis set
Number of subjects	90	90	82
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	36.5	36.5	
standard deviation	± 11.84	± 11.84	±
Gender categorical Units: Subjects			
Female	36	36	
Male	54	54	
Race Units: Subjects			
White	88	88	
Other	2	2	

Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	89	89	
Body mass index class Units: Subjects			
< 25 kg/m^2	41	41	
25-<30 kg/m^2	41	41	
30-<35 kg/m^2	6	6	
>=35 kg/m^2	2	2	
Height Units: centimeter(s)			
arithmetic mean	175.4	175.4	
standard deviation	± 10.10	± 10.10	±
Weight Units: kilogram(s)			
arithmetic mean	80.56	80.56	
standard deviation	± 16.265	± 16.265	±
Body mass index Units: kilogram(s)/square meter			
arithmetic mean	26.00	26.00	
standard deviation	± 3.669	± 3.669	±
Time since detection of diabetes Units: years			
arithmetic mean	18.86	18.86	
standard deviation	± 10.818	± 10.818	±

Reporting group values	Dasiglucagon Batch A (PP)	Dasiglucagon Batch B (PP)	
Number of subjects	82	82	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female			
Male			
Race Units: Subjects			
White			
Other			
Ethnicity Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Body mass index class Units: Subjects			
< 25 kg/m^2			

25-<30 kg/m^2 30-<35 kg/m^2 >=35 kg/m^2			
Height Units: centimeter(s) arithmetic mean standard deviation	±	±	
Weight Units: kilogram(s) arithmetic mean standard deviation	±	±	
Body mass index Units: kilogram(s)/square meter arithmetic mean standard deviation	±	±	
Time since detection of diabetes Units: years arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Dasiglucagon Batch A crossover to Dasiglucagon Batch B
Reporting group description:	
Single treatment with Dasiglucagon Batch A followed by cross-over to a single treatment with Dasiglucagon Batch B.	
Reporting group title	Dasiglucagon Batch B crossover to Dasiglucagon Batch A
Reporting group description:	
Single treatment with Dasiglucagon Batch B followed by cross-over to a single treatment with Dasiglucagon Batch A.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomly assigned patients who had received at least 1 dose of IMP.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomly assigned patients who had received at least 1 dose of IMP.	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of full analysis set who had received both treatments and had efficacy data available to evaluate the primary endpoint for both treatments. Patients could be excluded if relevant protocol deviations were documented (e.g. the use of prespecified concomitant medications).	
Subject analysis set title	Dasiglucagon Batch A (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of per protocol analysis set that received Batch A in either arm.	
Subject analysis set title	Dasiglucagon Batch B (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of per protocol analysis set that received Batch B in either arm.	

Primary: Time to plasma glucose recovery

End point title	Time to plasma glucose recovery
End point description:	
End point type	Primary
End point timeframe:	
From baseline to end of trial	

End point values	Dasiglucagon Batch A (PP)	Dasiglucagon Batch B (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82		
Units: minute				
arithmetic mean (standard deviation)	9.2 (± 2.34)	9.6 (± 2.89)		

Statistical analyses

Statistical analysis title	Non-inferiority of Batch B vs Batch A

Statistical analysis description:

Time to plasma glucose recovery was analyzed by an analysis of variance (ANOVA) model, including sequence, patient within sequence, period, and treatment as factors. The 2-sided 95% CI for the treatment difference was calculated from the ANOVA model.

Comparison groups	Dasiglucagon Batch A (PP) v Dasiglucagon Batch B (PP)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (net)
Point estimate	0.403
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.078
upper limit	0.884

Notes:

[1] - Non-inferiority of dasiglucagon Batch B relative to that of dasiglucagon Batch A was concluded as the upper limit of the 2-sided 95% CI of the treatment difference between Batch A and Batch B did not exceed δ=2 min.

Secondary: Plasma Glucose Change from Baseline

End point title	Plasma Glucose Change from Baseline

End point description:

End point type	Secondary

End point timeframe:

From baseline to end of trial

End point values	Dasiglucagon Batch A (PP)	Dasiglucagon Batch B (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	82		
Units: milligram(s)/decilitre				
arithmetic mean (standard deviation)				
10 minutes post-dose	24.603 (± 9.8296)	24.166 (± 10.9019)		
15 minutes post-dose	45.436 (± 13.9841)	44.441 (± 15.2431)		
20 minutes post-dose	63.423 (± 17.8243)	63.067 (± 17.8480)		
30 minutes post-dose	92.817 (± 23.2345)	93.999 (± 22.6758)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All AEs and SAEs were collected from the signing of the informed consent form and until the end of the posttreatment follow-up period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Batch A
Reporting group description:	
Subjects from the safety analysis set that received Batch A in either arm.	
Reporting group title	Batch B
Reporting group description:	
Subjects in the safety analysis set that received Batch B in either arm.	

Serious adverse events	Batch A	Batch B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 87 (0.00%)	0 / 87 (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: 5 %

Non-serious adverse events	Batch A	Batch B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 87 (77.01%)	64 / 87 (73.56%)	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 87 (8.05%)	3 / 87 (3.45%)	
occurrences (all)	7	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	61 / 87 (70.11%)	59 / 87 (67.82%)	
occurrences (all)	65	61	
Vomiting			

subjects affected / exposed occurrences (all)	30 / 87 (34.48%) 31	26 / 87 (29.89%) 32	
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 11 / 87 (12.64%) 12	 11 / 87 (12.64%) 16	

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