Clinical trial results:
A randomised, sequential, cross-over trial assessing pharmacokinetic and pharmacodynamic responses after micro-doses of ZP4207 administered subcutaneously to patients with type 1 diabetes mellitus under euglycaemic and hypoglycaemic conditions and with reference to freshly reconstituted lyophilized glucagon

Summary

EudraCT number	2016-002617-21
Trial protocol	DE
Global end of trial date	05 April 2017

Results information

Result version number	v1 (current)
This version publication date	29 July 2020
First version publication date	29 July 2020

Trial information

Trial identification

Sponsor protocol code	ZP4207-16098

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02916251
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zealand Pharma
Sponsor organisation address	Sydmarken 11, Søborg, Denmark, 2860
Public contact	Dorte Skydsgaard, Zealand Pharma A/S, +45 5060 3767, DSkydsgaard@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	06 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2017
Global end of trial reached?	Yes
Global end of trial date	05 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the PK and PD properties of ZP4207 4 mg/mL following s.c. administration at euglycemic and hypoglycemic conditions in adult patients with 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	01 December 2016
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	Germany: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from a single site in Germany.

Pre-assignment

Screening details:

40 patients were screened and 23 patients were eligible and randomised.

Period 1

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

Blinding implementation details:

For the 3 lowest dose levels (0.03 mg, 0.08 mg and 0.2 mg), the patients received 1 ZP4207 dose and 1 Glucagon™ dose at euglycemic conditions on Day 1, while 1 ZP4207 dose was administered at hypoglycemic conditions on Day 2 (Visits 2-4). Patients were randomised to one of 6 treatment sequences (different order of the three lowest dose levels as well as the order of ZP4207 and Glucagon on day 1). All patients received 2 administrations of ZP4207 0.6 mg (euglycemic then hypoglycemic) at Visit 5.

Arms

Are arms mutually exclusive?	No
Arm title	0.03 mg ZP4207 - euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.03 mg ZP4207 at euglycemic state however at different trial visits.

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.03 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.03 mg ZP4207 in solution was administered via disposable dosing syringe. The subcutaneous injections was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.08 mg ZP4207 - euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.08 mg ZP4207 at euglycemic state however at different trial visits.

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.08 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.08 mg of ZP4207 was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.2 mg ZP4207 - euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.2 mg ZP4207 at euglycemic state however at different trial visits

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.2 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.2 mg ZP4207 in solution was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.6 mg ZP4207 - euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.6 mg ZP4207 at euglycemic state, however at different trial visits

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.6 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.6 mg ZP4207 in solution was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.03 mg ZP4207 - hypoglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.03 mg ZP4207 at hypoglycemic state, however at different trial visits

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.03 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.03 mg ZP4207 in solution was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.08 mg ZP4207 - hypoglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.08 mg ZP4207 at hypoglycemic state, however at different trial visits

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.08 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.08 mg of ZP4207 was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.2 mg ZP4207 - hypoglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.2 mg ZP4207 at hyopglycemic state, however at different trial visits

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.2 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.2 mg ZP4207 in solution was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.6 mg ZP4207 - hypoglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.6 mg ZP4207 at hypoglycemic state, however at different trial visits

Arm type	Experimental
Investigational medicinal product name	ZP4207 - 0.6 mg
Investigational medicinal product code	
Other name	Dasiglucagon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.6 mg ZP4207 in solution was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.03 mg Lilly Glucagon - euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.03 mg Lilly Glucagon at euglycemic state, however at different trial visits

Arm type	Active comparator
Investigational medicinal product name	Lilly Glucagon - 0.03 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.03 mg Glucagon was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.08 mg Lilly Glucagon - euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.08 mg Lilly Glucagon at euglycemic state, however at different trial visits

Arm type	Active comparator
Investigational medicinal product name	Lilly Glucagon - 0.08 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.08 mg Glucagon was administered via disposable dosing syringe. The subcutaneous

injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Arm title	0.2 mg Lilly Glucagon - Euglycemic condition

Arm description:

Due to the design of the trial all patients received one dose of 0.2 mg Lilly Glucagon at euglycemic state, however at different trial visits

Arm type	Active comparator
Investigational medicinal product name	Lilly Glucagon - 0.2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of 0.2 mg Glucagon was administered via disposable dosing syringe. The subcutaneous injection was given into the abdominal skin in the peri-umbilical area by trained personnel.

Number of subjects in period 1	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition
Started	16	17	16
Completed	16	17	16

Number of subjects in period 1	0.6 mg ZP4207 - euglycemic condition	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition
Started	17	17	17
Completed	17	17	17

Number of subjects in period 1	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition	0.03 mg Lilly Glucagon - euglycemic condition
Started	17	17	17
Completed	17	17	17

Number of subjects in period 1	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition
Started	17	16
Completed	17	16

Baseline characteristics

Reporting groups	
Reporting group title	Overall
Reporting group description:	
Safety analysis set - all patients exposed	

Reporting group values	Overall	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
Adults (18-64 years)	23	23	
Age continuous Units: years			
arithmetic mean	44.2		
standard deviation	± 13.07	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	14	14	
Height Units: centimetre			
arithmetic mean	176.26		
standard deviation	± 7.442	-	
Weight Units: kilogram(s)			
arithmetic mean	78.24		
standard deviation	± 9.311	-	
BMI Units: kilogram(s)/square meter			
arithmetic mean	25.21		
standard deviation	± 2.927	-	
HbA1c Units: percent			
arithmetic mean	7.42		
standard deviation	± 0.578	-	

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set consist of patients enrolled according to protocol amendment 3.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set includes all patients receiving at least one dose of the IMP (including the first 6 patients).	

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	17	23	
Age categorical Units: Subjects			
Adults (18-64 years)	17	23	
Age continuous Units: years			
arithmetic mean	41.9	44.2	
standard deviation	± 14.21	± 13.07	
Gender categorical Units: Subjects			
Female	7	9	
Male	10	14	
Height Units: centimetre			
arithmetic mean	176.24	176.26	
standard deviation	± 6.6945	± 7.442	
Weight Units: kilogram(s)			
arithmetic mean	79.52	78.24	
standard deviation	± 8.613	± 9.311	
BMI Units: kilogram(s)/square meter			
arithmetic mean	25.65	25.21	
standard deviation	± 3.061	± 2.927	
HbA1c Units: percent			
arithmetic mean	7.48	7.42	
standard deviation	± 0.472	± 0.578	

End points

End points reporting groups

Reporting group title	0.03 mg ZP4207 - euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.03 mg ZP4207 at euglycemic state however at different trial visits.	
Reporting group title	0.08 mg ZP4207 - euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.08 mg ZP4207 at euglycemic state however at different trial visits.	
Reporting group title	0.2 mg ZP4207 - euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.2 mg ZP4207 at euglycemic state however at different trial visits	
Reporting group title	0.6 mg ZP4207 - euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.6 mg ZP4207 at euglycemic state, however at different trial visits	
Reporting group title	0.03 mg ZP4207 - hypoglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.03 mg ZP4207 at hypoglycemic state, however at different trial visits	
Reporting group title	0.08 mg ZP4207 - hypoglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.08 mg ZP4207 at hypoglycemic state, however at different trial visits	
Reporting group title	0.2 mg ZP4207 - hypoglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.2 mg ZP4207 at hyopglycemic state, however at different trial visits	
Reporting group title	0.6 mg ZP4207 - hypoglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.6 mg ZP4207 at hypoglycemic state, however at different trial visits	
Reporting group title	0.03 mg Lilly Glucagon - euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.03 mg Lilly Glucagon at euglycemic state, however at different trial visits	
Reporting group title	0.08 mg Lilly Glucagon - euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.08 mg Lilly Glucagon at euglycemic state, however at different trial visits	
Reporting group title	0.2 mg Lilly Glucagon - Euglycemic condition
Reporting group description:	
Due to the design of the trial all patients received one dose of 0.2 mg Lilly Glucagon at euglycemic state, however at different trial visits	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set consist of patients enrolled according to protocol amendment 3.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set includes all patients receiving at least one dose of the IMP (including the first 6 patients).

Primary: Pharmacokinetics - Area under the plasma concentration curve (0-240 minutes)

End point title	Pharmacokinetics - Area under the plasma concentration curve (0-240 minutes)

End point description:

AUC(0-240min), area under the plasma ZP4207 and baseline adjusted plasma glucagon concentration curve from 0 to 240 minutes post-dose

End point type	Primary

End point timeframe:

From dosing and untill 240 minutes post-dose

End point values	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition	0.6 mg ZP4207 - euglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	17
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	169 (± 25.1)	549 (± 23.3)	1260 (± 19.6)	3570 (± 16.5)

End point values	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	168 (± 24.7)	589 (± 21.5)	1280 (± 16.3)	3490 (± 20.3)

End point values	0.03 mg Lilly Glucagon - euglycemic condition	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	16	
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	49.8 (± 39.0)	129 (± 26.4)	349 (± 30.7)	

Statistical analyses

Statistical analysis title	AUC(0-240min) - ZP4207/Lilly Glucagon - 0.03 mg
Statistical analysis description:	
Comparison of AUC (0-240 min) for 0.03 mg ZP4207 vs 0.03 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.03 mg Lilly Glucagon - euglycemic condition v 0.03 mg ZP4207 - euglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	least squares mean ratio
Point estimate	3.37
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.95
upper limit	3.84

Notes:

[1] - No defined H0-hypothesis

Statistical analysis title	AUC(0-240min) - ZP4207/Lilly Glucagon - 0.08 mg
Statistical analysis description:	
Comparison of AUC (0-240 min) for 0.08 mg ZP4207 vs 0.08 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	least squares mean ratio
Point estimate	4.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.75
upper limit	4.86

Notes:

[2] - No defined H0-hypothesis

Statistical analysis title	AUC(0-240min) - ZP4207/Lilly Glucagon - 0.2 mg
Statistical analysis description:	
Comparison of AUC (0-240 min) for 0.2 mg ZP4207 vs 0.2 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg Lilly Glucagon - Euglycemic condition
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	least squares mean ratio
Point estimate	3.62

Confidence interval	
level	90 %
sides	2-sided
lower limit	3.17
upper limit	4.14

Notes:

[3] - No defined H0-hypothesis

Statistical analysis title	AUC(0-240min) - ZP4207 Eugly/hypogly state 0.03 mg
Statistical analysis description:	
Comparison of AUC (0-240 min) for 0.03 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	least squares mean ratio
Point estimate	0.993
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.916
upper limit	1.077

Notes:

[4] - No defined H0-hypothesis

Statistical analysis title	AUC(0-240min) - ZP4207 Eugly/hypogly state 0.08 mg
Statistical analysis description:	
Comparison of AUC (0-240 min) for 0.08 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	least squares mean ratio
Point estimate	0.931
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.86
upper limit	1.009

Notes:

[5] - No defined H0-hypothesis

Statistical analysis title	AUC(0-240min) - ZP4207 Eugly/hypogly state 0.2 mg
Statistical analysis description:	
Comparison of AUC (0-240 min) for 0.2 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg ZP4207 - hypoglycemic condition

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	least squares mean ratio
Point estimate	0.986
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.909
upper limit	1.07

Notes:

[6] - No defined H0-hypothesis

Statistical analysis title	AUC(0-240min) - ZP4207 Eugly/hypogly state 0.6 mg

Statistical analysis description:

Comparison of AUC (0-240 min) for 0.6 mg ZP4207 at euglycemic vs hypoglycemic condition

Comparison groups	0.6 mg ZP4207 - euglycemic condition v 0.6 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	least squares mean ratio
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.968
upper limit	1.076

Notes:

[7] - No defined H0-hypothesis

Primary: Pharmacokinetics - Cmax

End point title	Pharmacokinetics - Cmax

End point description:

Cmax,maximum of all valid plasma ZP4207 and baseline adjusted plasma glucagon concentration measurements from 0 to 240 minutes post-dose

End point type	Primary

End point timeframe:

From dosing and untill 240 minutes post-dose

End point values	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition	0.6 mg ZP4207 - euglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	17
Units: picomol/L				
geometric mean (geometric coefficient of variation)	142 (± 33.6)	387 (± 31.8)	733 (± 33.2)	1970 (± 25.9)

End point values	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: picomol/L				
geometric mean (geometric coefficient of variation)	129 (± 33.5)	422 (± 38.8)	810 (± 22.7)	1940 (± 26.0)

End point values	0.03 mg Lilly Glucagon - euglycemic condition	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	16	
Units: picomol/L				
geometric mean (geometric coefficient of variation)	74.7 (± 42.8)	160 (± 29.2)	420 (± 30.2)	

Statistical analyses

Statistical analysis title	Cmax - ZP4207/Lilly Glucagon 0.03 mg
Statistical analysis description:	
Comparison of Cmax for 0.03 mg ZP4207 vs 0.03 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Cmax Ratio
Point estimate	1.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.64
upper limit	2.18

Notes:

[8] - Descriptive analysis

Statistical analysis title	Cmax - ZP4207/Lilly Glucagon 0.08 mg
Statistical analysis description:	
Comparison of Cmax for 0.08 mg ZP4207 vs 0.08 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg Lilly Glucagon - euglycemic condition

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Cmax Ratio
Point estimate	2.42
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.1
upper limit	2.78

Notes:

[9] - Descriptive analysis

Statistical analysis title	Cmax - ZP4207/Lilly Glucagon 0.2 mg

Statistical analysis description:

Comparison of Cmax for 0.08 mg ZP4207 vs 0.08 mg Lilly Glucagon at euglycemic condition

Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg Lilly Glucagon - Euglycemic condition
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Cmax Ratio
Point estimate	1.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.51
upper limit	2.02

Notes:

[10] - Descriptive analysis

Statistical analysis title	Cmax - ZP4207 Eugly/hypogly state 0.03 mg

Statistical analysis description:

Comparison of Cmax for 0.03 mg ZP4207 at euglycemic vs hypoglycemic condition

Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Cmax Ratio
Point estimate	1.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.23

Notes:

[11] - Descriptive analysis

Statistical analysis title	Cmax - ZP4207 Eugly/hypogly state 0.08 mg

Statistical analysis description:	
Comparison of Cmax for 0.08 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Cmax Ratio
Point estimate	0.918
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.807
upper limit	1.043

Notes:

[12] - Descriptive analysis

Statistical analysis title	Cmax - ZP4207 Eugly/hypogly state 0.2 mg
Statistical analysis description:	
Comparison of Cmax for 0.2mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Cmax Ratio
Point estimate	0.914
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.802
upper limit	1.041

Notes:

[13] - Descriptive analysis

Statistical analysis title	Cmax - ZP4207 Eugly/hypogly state 0.6 mg
Statistical analysis description:	
Comparison of Cmax for 0.6 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.6 mg ZP4207 - euglycemic condition v 0.6 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Cmax Ratio
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.915
upper limit	1.117

Notes:
[14] - Descriptive analysis

Primary: Pharmacokinetics - Tmax

End point title	Pharmacokinetics - Tmax

End point description:
tmax, time to maximum of plasma ZP4207 and baseline adjusted plasma glucagon concentration measurements

End point type	Primary

End point timeframe:
From dosing and untill 240 minutes post-dose

End point values	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition	0.6 mg ZP4207 - euglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	17
Units: hour				
median (full range (min-max))	0.500 (0.25 to 1.00)	0.500 (0.25 to 1.50)	0.500 (0.50 to 1.50)	0.500 (0.25 to 1.00)

End point values	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: hour				
median (full range (min-max))	0.500 (0.25 to 1.00)	0.500 (0.25 to 1.00)	0.500 (0.25 to 1.00)	0.500 (0.25 to 1.00)

End point values	0.03 mg Lilly Glucagon - euglycemic condition	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	16	
Units: hour				
median (full range (min-max))	0.250 (0.08 to 0.50)	0.250 (0.25 to 0.50)	0.250 (0.25 to 0.50)	

Statistical analyses

Statistical analysis title	Estimate of diff. - ZP4207/Lilly Glucagon 0.03 mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Lilly GlucagonTM) according to Hodges and Lehmann	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[15]
Parameter estimate	Point estimate of difference
Point estimate	0.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	0.25

Notes:

[15] - Descriptive analysis

Statistical analysis title	Estimate of diff. - ZP4207/Lilly Glucagon 0.08 mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Lilly GlucagonTM) according to Hodges and Lehmann	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	Point estimate of difference
Point estimate	0.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	0.25

Notes:

[16] - Descriptive analysis

Statistical analysis title	Estimate of diff. - ZP4207/Lilly Glucagon 0.2mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Lilly GlucagonTM) according to Hodges and Lehmann	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg Lilly Glucagon - Euglycemic condition
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[17]
Parameter estimate	Point estimate of difference
Point estimate	0.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	0.5

Notes:

[17] - Descriptive analysis

Statistical analysis title	Estimate of diff ZP4207 eugly/hypogly state 0.03mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Euglycemic vs Hypoglycemic state) according to Hodges and Lehmann	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[18]
Parameter estimate	Point estimate of difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.25
upper limit	0

Notes:

[18] - Descriptive analysis

Statistical analysis title	Estimate of diff ZP4207 eugly/hypogly state 0.08mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Euglycemic vs Hypoglycemic state) according to Hodges and Lehmann	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[19]
Parameter estimate	Point estimate of difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[19] - Descriptive analysis

Statistical analysis title	Estimate of diff ZP4207 eugly/hypogly state 0.2mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Euglycemic vs Hypoglycemic state) according to Hodges and Lehmann	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg ZP4207 - hypoglycemic condition

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[20]
Parameter estimate	Point estimate of difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[20] - Descriptive analysis

Statistical analysis title	Estimate of diff ZP4207 eugly/hypogly state 0.6mg

Statistical analysis description:

Point estimate of median of differences (ZP4207 - Euglycemic vs Hypoglycemic state) according to Hodges and Lehmann

Comparison groups	0.6 mg ZP4207 - euglycemic condition v 0.6 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[21]
Parameter estimate	Point estimate of difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[21] - Descriptive analysis

Primary: Pharmacodynamics - Area under the effect curve (0-240 minutes)

End point title	Pharmacodynamics - Area under the effect curve (0-240 minutes)

End point description:

End point type	Primary

End point timeframe:

Baseline to 4 hours after dose

End point values	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition	0.6 mg ZP4207 - euglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	17
Units: mg.h/L				
arithmetic mean (standard deviation)	105 (± 87.9)	242 (± 149)	386 (± 146)	479 (± 159)

End point values	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mg.h/L				
arithmetic mean (standard deviation)	70.6 (± 100)	249 (± 201)	406 (± 175)	535 (± 187)

End point values	0.03 mg Lilly Glucagon - euglycemic condition	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	16	
Units: mg.h/L				
arithmetic mean (standard deviation)	49.7 (± 53.3)	112 (± 102)	179 (± 115)	

Statistical analyses

Statistical analysis title	AUE(0-240min) - ZP4207/Lilly Glucagon - 0.03 mg
Statistical analysis description:	
Comparison of AUE (0-240 min) for 0.03 mg ZP4207 vs 0.03 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[22]
Parameter estimate	least squares mean ratio
Point estimate	2.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.3058
upper limit	3.9042

Notes:

[22] - No defined H0-hypothesis

Statistical analysis title	AUE(0-240min) - ZP4207/Lilly Glucagon - 0.08 mg
Statistical analysis description:	
Comparison of AUE (0-240 min) for 0.08 mg ZP4207 vs 0.08 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg Lilly Glucagon - euglycemic condition

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[23]
Parameter estimate	least squares mean ratio
Point estimate	4.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.4691
upper limit	6.7835

Notes:

[23] - No defined H0-hypothesis

Statistical analysis title	AUE(0-240min) - ZP4207/Lilly Glucagon - 0.2 mg

Statistical analysis description:

Comparison of AUE (0-240 min) for 0.2 mg ZP4207 vs 0.2 mg Lilly Glucagon at euglycemic condition

Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg Lilly Glucagon - Euglycemic condition
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[24]
Parameter estimate	least squares mean ratio
Point estimate	2.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.4434
upper limit	4.1772

Notes:

[24] - No defined H0-hypothesis

Statistical analysis title	AUE(0-240min) - ZP4207 Eugly/hypogly state 0.03 mg

Statistical analysis description:

Comparison of AUE (0-240 min) for 0.03 mg ZP4207 at euglycemic vs hypoglycemic condition

Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[25]
Parameter estimate	least squares mean ratio
Point estimate	2.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2481
upper limit	3.3907

Notes:

[25] - No defined H0-hypothesis

Statistical analysis title	AUE(0-240min) - ZP4207 Eugly/hypogly state 0.08 mg

Statistical analysis description:	
Comparison of AUE (0-240 min) for 0.08 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[26]
Parameter estimate	least squares mean ratio
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7153
upper limit	2.036

Notes:

[26] - No defined H0-hypothesis

Statistical analysis title	AUE(0-240min) - ZP4207 Eugly/hypogly state 0.2 mg
Statistical analysis description:	
Comparison of AUE (0-240 min) for 0.2 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[27]
Parameter estimate	least squares mean ratio
Point estimate	0.865
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5075
upper limit	1.4748

Notes:

[27] - No defined H0-hypothesis

Statistical analysis title	AUE(0-240min) - ZP4207 Eugly/hypogly state 0.6 mg
Statistical analysis description:	
Comparison of AUE (0-240 min) for 0.6 mg ZP4207 at euglycemic vs hypoglycemic condition	
Comparison groups	0.6 mg ZP4207 - euglycemic condition v 0.6 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[28]
Parameter estimate	least squares mean ratio
Point estimate	0.908
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7408
upper limit	1.1128

Notes:

[28] - No defined H0-hypothesis

Primary: Pharmacodynamics - CEmax

End point title	Pharmacodynamics - CEmax

End point description:

PD endpoints were derived from the plasma glucose profiles above baseline, where baseline was defined as the pre-dose measurement prior to each dosing. The endpoints were calculated in accordance with model 220 of Phoenix/WinNonLin.

End point type	Primary

End point timeframe:

Baseline to 4 hours after dose

End point values	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition	0.6 mg ZP4207 - euglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	17
Units: mg/dL				
arithmetic mean (standard deviation)	54.0 (± 32.9)	101 (± 44.4)	139 (± 42.7)	165 (± 46.1)

End point values	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: mg/dL				
arithmetic mean (standard deviation)	37.9 (± 38.9)	106 (± 61.1)	154 (± 48.4)	192 (± 54.1)

End point values	0.03 mg Lilly Glucagon - euglycemic condition	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	15	
Units: mg/dL				
arithmetic mean (standard deviation)	32.6 (± 25.2)	59.5 (± 36.3)	86.1 (± 38.2)	

Statistical analyses

Statistical analysis title	CEmax - ZP4207/Lilly Glucagon - 0.03 mg

Statistical analysis description:	
Comparison of CEmax for 0.03 mg ZP4207 vs 0.03 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[29]
Parameter estimate	least squares mean ratio
Point estimate	1.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1865
upper limit	1.8132

Notes:

[29] - No defined H0-hypothesis

Statistical analysis title	CEmax - ZP4207 Eugly/hypogly state 0.08 mg
Statistical analysis description:	
Comparison of CEmax for 0.08 mg ZP4207 vs 0.08 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[30]
Parameter estimate	least squares mean ratio
Point estimate	1.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.5175
upper limit	2.253

Notes:

[30] - No defined H0-hypothesis

Statistical analysis title	CEmax - ZP4207/Lilly Glucagon - 0.2 mg
Statistical analysis description:	
Comparison of CEmax for 0.2 mg ZP4207 vs 0.2 mg Lilly Glucagon at euglycemic condition	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg Lilly Glucagon - Euglycemic condition
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[31]
Parameter estimate	least squares mean ratio
Point estimate	1.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.3767
upper limit	2.0687

Notes:

[31] - No defined H0-hypothesis

Statistical analysis title	CEmax - ZP4207 Eugly/hypogly state 0.03 mg

Statistical analysis description:

Analysis of variance (ANOVA) with log-transformed response, glycemic state, dose, their interaction, period, sequence and patient within sequence as fixed effects. Point estimate is the ratio of geometric LS-means of glycemic states (euglycemic/hypoglycemic) for the 0.03mg dose.

Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[32]
Parameter estimate	least squares mean ratio
Point estimate	1.65
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1848
upper limit	2.2855

Notes:

[32] - No defined H0-hypothesis

Statistical analysis title	CEmax - ZP4207 Eugly/hypogly state 0.08 mg

Statistical analysis description:

Analysis of variance (ANOVA) with log-transformed response, glycemic state, dose, their interaction, period, sequence and patient within sequence as fixed effects. Point estimate is the ratio of geometric LS-means of glycemic states (euglycemic/hypoglycemic) for the 0.08mg dose.

Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[33]
Parameter estimate	least squares mean ratio
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7559
upper limit	1.3761

Notes:

[33] - No defined H0-hypothesis

Statistical analysis title	CEmax - ZP4207 Eugly/hypogly state 0.2 mg

Statistical analysis description:

Analysis of variance (ANOVA) with log-transformed response, glycemic state, dose, their interaction, period, sequence and patient within sequence as fixed effects. Point estimate is the ratio of geometric LS-means of glycemic states (euglycemic/hypoglycemic) for the 0.2mg dose.

Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg ZP4207 - hypoglycemic condition

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[34]
Parameter estimate	least squares mean ratio
Point estimate	0.838
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.6174
upper limit	1.1375

Notes:

[34] - No defined H0-hypothesis

Statistical analysis title	CEmax - ZP4207 Eugly/hypogly state 0.6 mg

Statistical analysis description:

Analysis of variance (ANOVA) with log-transformed response, glycemic state and patient as fixed effect. Point estimate is the ratio of geometric LS-means of glycemic states (euglycemic/hypoglycemic) for the 0.6mg dose.

Comparison groups	0.6 mg ZP4207 - euglycemic condition v 0.6 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[35]
Parameter estimate	least squares mean ratio
Point estimate	0.859
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7597
upper limit	0.9722

Notes:

[35] - No defined H0-hypothesis

Primary: Pharmacodynamics - TEmax

End point title	Pharmacodynamics - TEmax

End point description:

End point type	Primary

End point timeframe:

Baseline to 4 hours after dose

End point values	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition	0.6 mg ZP4207 - euglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	17	16	17
Units: minute				
arithmetic mean (standard deviation)	56.9 (± 24.4)	84.1 (± 27.2)	98.8 (± 31.8)	119 (± 43.6)

End point values	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	17	17
Units: minute				
arithmetic mean (standard deviation)	45.9 (± 27.4)	69.0 (± 16.6)	87.6 (± 25.4)	102 (± 28.3)

End point values	0.03 mg Lilly Glucagon - euglycemic condition	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	15	
Units: minute				
arithmetic mean (standard deviation)	32.9 (± 19.6)	43.5 (± 19.7)	52.7 (± 18.3)	

Statistical analyses

Statistical analysis title	TEmax - ZP4207/Lilly Glucagon - 0.03 mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Lilly GlucagonTM) for 0.03mg dose according to Hodges and Lehmann	
Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg Lilly Glucagon - euglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[36]
Parameter estimate	Median difference (final values)
Point estimate	20
Confidence interval	
level	90 %
sides	2-sided
lower limit	20
upper limit	40

Notes:

[36] - No defined H0-hypothesis

Statistical analysis title	TEmax - ZP4207/Lilly Glucagon - 0.08 mg
Statistical analysis description:	
Point estimate of median of differences (ZP4207 - Lilly GlucagonTM) for 0.08mg dose according to Hodges and Lehmann	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg Lilly Glucagon - euglycemic condition

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[37]
Parameter estimate	Median difference (final values)
Point estimate	40
Confidence interval	
level	90 %
sides	2-sided
lower limit	20
upper limit	40

Notes:

[37] - No defined H0-hypothesis

Statistical analysis title	TEmax - ZP4207/Lilly Glucagon - 0.2 mg

Statistical analysis description:

Point estimate of median of differences (ZP4207 - Lilly GlucagonTM) for 0.2mg dose according to Hodges and Lehmann

Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg Lilly Glucagon - Euglycemic condition
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[38]
Parameter estimate	Median difference (final values)
Point estimate	40
Confidence interval	
level	90 %
sides	2-sided
lower limit	20
upper limit	60

Notes:

[38] - No defined H0-hypothesis

Statistical analysis title	TEmax - ZP4207 Eugly/hypogly state 0.03 mg

Statistical analysis description:

Point estimate of median of differences (euglycemic - hypoglycemic) for the 0.03mg dose according to Hodges and Lehmann

Comparison groups	0.03 mg ZP4207 - euglycemic condition v 0.03 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[39]
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[39] - No defined H0-hypothesis

Statistical analysis title	TEmax - ZP4207 Eugly/hypogly state 0.08 mg
Statistical analysis description:	
Point estimate of median of differences (euglycemic - hypoglycemic) for the 0.08mg dose according to Hodges and Lehmann	
Comparison groups	0.08 mg ZP4207 - euglycemic condition v 0.08 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[40]
Parameter estimate	Median difference (final values)
Point estimate	17
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[40] - No defined H0-hypothesis

Statistical analysis title	TEmax - ZP4207 Eugly/hypogly state 0.2 mg
Statistical analysis description:	
Point estimate of median of differences (euglycemic - hypoglycemic) for the 0.2mg dose according to Hodges and Lehmann	
Comparison groups	0.2 mg ZP4207 - euglycemic condition v 0.2 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[41]
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[41] - No defined H0-hypothesis

Statistical analysis title	TEmax - ZP4207 Eugly/hypogly state 0.6 mg
Statistical analysis description:	
Point estimate of median of differences (euglycemic - hypoglycemic) for the 0.6mg dose according to Hodges and Lehmann	
Comparison groups	0.6 mg ZP4207 - euglycemic condition v 0.6 mg ZP4207 - hypoglycemic condition
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[42] - No defined H0-hypothesis

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	20.0

Reporting groups

Reporting group title	0.03 mg ZP4207 - euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.03 mg ZP4207 at euglycemic state however at different trial visits.

Reporting group title	0.08 mg ZP4207 - euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.08 mg ZP4207 at euglycemic state however at different trial visits.

Reporting group title	0.2 mg ZP4207 - euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.2 mg ZP4207 at euglycemic state however at different trial visits

Reporting group title	0.6 mg ZP4207 - euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.03 mg ZP4207 at euglycemic state, however at different trial visits

Reporting group title	0.03 mg ZP4207 - hypoglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.03 mg ZP4207 at hypoglycemic state, however at different trial visits

Reporting group title	0.08 mg ZP4207 - hypoglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.08 mg ZP4207 at hypoglycemic state, however at different trial visits

Reporting group title	0.2 mg ZP4207 - hypoglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.2 mg ZP4207 at hyopglycemic state, however at different trial visits

Reporting group title	0.6 mg ZP4207 - hypoglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.6 mg ZP4207 at hypoglycemic state, however at different trial visits

Reporting group title	0.03 mg Lilly Glucagon - euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.03 mg Lilly Glucagon at euglycemic state, however at different trial visits

Reporting group title	0.08 mg Lilly Glucagon - euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.08 mg Lilly Glucagon at euglycemic state, however at different trial visits

Reporting group title	0.2 mg Lilly Glucagon - Euglycemic condition

Reporting group description:

Due to the design of the trial all patients recieved one dose of 0.2 mg Lilly Glucagon at euglycemic

Serious adverse events	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	0.6 mg ZP4207 - euglycemic condition	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition	0.03 mg Lilly Glucagon - euglycemic condition
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	0.03 mg ZP4207 - euglycemic condition	0.08 mg ZP4207 - euglycemic condition	0.2 mg ZP4207 - euglycemic condition
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	7 / 20 (35.00%)	12 / 20 (60.00%)
Injury, poisoning and procedural complications			
Application site haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Orthostatic intolerance			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site oedema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Nausea			

subjects affected / exposed	1 / 20 (5.00%)	5 / 20 (25.00%)	11 / 20 (55.00%)
occurrences (all)	1	5	11
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	5 / 20 (25.00%)
occurrences (all)	1	2	5
Respiratory, thoracic and mediastinal disorders			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	0.6 mg ZP4207 - euglycemic condition	0.03 mg ZP4207 - hypoglycemic condition	0.08 mg ZP4207 - hypoglycemic condition
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 17 (58.82%)	4 / 20 (20.00%)	6 / 20 (30.00%)
Injury, poisoning and procedural complications			
Application site haematoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 17 (5.88%)	1 / 20 (5.00%)	2 / 20 (10.00%)
occurrences (all)	1	1	2
Orthostatic intolerance			
subjects affected / exposed	1 / 17 (5.88%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site oedema			

subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	8 / 17 (47.06%)	2 / 20 (10.00%)	2 / 20 (10.00%)
occurrences (all)	8	2	2
Toothache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 17 (17.65%)	1 / 20 (5.00%)	2 / 20 (10.00%)
occurrences (all)	3	1	3
Respiratory, thoracic and mediastinal disorders			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	0.2 mg ZP4207 - hypoglycemic condition	0.6 mg ZP4207 - hypoglycemic condition	0.03 mg Lilly Glucagon - euglycemic condition
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	9 / 17 (52.94%)	3 / 21 (14.29%)
Injury, poisoning and procedural complications			
Application site haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 20 (10.00%)	1 / 17 (5.88%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Orthostatic intolerance			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Injection site oedema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	5 / 20 (25.00%)	7 / 17 (41.18%)	0 / 21 (0.00%)
occurrences (all)	5	7	0
Toothache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)	4 / 17 (23.53%)	0 / 21 (0.00%)
occurrences (all)	2	4	0
Respiratory, thoracic and mediastinal disorders			

Viral upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 17 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	0.08 mg Lilly Glucagon - euglycemic condition	0.2 mg Lilly Glucagon - Euglycemic condition	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	6 / 20 (30.00%)	
Injury, poisoning and procedural complications			
Application site haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	1 / 20 (5.00%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Orthostatic intolerance			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Injection site oedema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Injection site pruritus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 20 (5.00%)	4 / 20 (20.00%)	
occurrences (all)	1	4	
Toothache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2016	This amendment was created after blinded review of PD data of the first 6 patients. Glucagon action was found to be difficult to assess due to a too high insulin infusion rate before and during the clamp procedure. To address this issue the following changes were introduced: • the i.v. insulin infusion rate was reduced and made more flexible to better match individual patients' needs. • the threshold for initiation of the i.v. glucose infusion during the euglycemic clamp assessment was increased to avoid time in hypoglycemia. • the first 6 patients were withdrawn from the trial (impact on statistical analysis could not be ruled out due to possible glucose counter-regulatory responses to hypoglycemia). Five (5) of these patients were withdrawn as per Investigator's decision, and one patient who belonged also to the group of patients meeting the criteria for exclusion described in the protocol amendment actually decided on own initiative to discontinue the trial. The withdrawn patients did not continue the trial but attended a complete follow-up examination in accordance with the protocol. • since the 6 patients needed to be replaced to have at least 15 completers, replacement and re-screening criteria in the protocol were modified. o new patients received the same randomization/treatment sequence as the initial 6 patients. o replacements were performed to ensure that at least 15 patients complete Visit 5 with sufficient evaluable data to perform statistical analysis. o re-screening of eligible patients (who were not yet randomized) was possible. In that case, a new informed consent had to be signed and dated. • the primary endpoint (AUE0-240min) was explained to be calculated up to the last measurement prior to intervention in case of premature glucose infusion intervention. • PK/PD data for these first 6 patients were reported separately. Data from the first 6 patients were excluded from FAS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30350477