Clinical trial results:
A Two-Period, Open-label Trial Evaluating the Efficacy and Safety of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism

Summary

EudraCT number	2017-004547-21
Trial protocol	GB DE
Global end of trial date	05 October 2020

Results information

Result version number	v2 (current)
This version publication date	28 December 2023
First version publication date	04 August 2021
Version creation reason	• Correction of full data set The clinical study report was corrected; the corrections are reflected in this version of the results.

Trial information

Trial identification

Sponsor protocol code	ZP4207-17109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03777176
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zealand Pharma A/S
Sponsor organisation address	Sydmarken 11, Søborg, Denmark, 2860
Public contact	Sune Birch, Principal Biostatistician, Zealand Pharma A/S, 45 88 77 36 00, SBirch@zealandpharma.com
Scientific contact	Sune Birch, Principal Biostatistician, Zealand Pharma A/S, 45 88 77 36 00, SBirch@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	15 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	Yes
Global end of trial date	05 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of dasiglucagon administered as a subcutaneous (SC) infusion in reducing hypoglycemia in children with Congenital Hyperinsulinism.

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	07 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	32
EEA total number of subjects	6

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)	9
Children (2-11 years)	23
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at a total of 11 sites in the USA (4 sites), UK (4 sites), Germany (2 sites), and Israel (1 site).

Pre-assignment

Screening details:

A total of 35 patients were screened of which 32 patients were randomized.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dasiglucagon + standard of care

Arm description:

In Treatment Period 1 (Weeks 1 to 4), patients in this arm received standard of care + dasiglucagon for 4 weeks. Standard of care treatment could include most drugs commonly used and/or recommended in treatment of congenital hyperinsulinism (CHI) including, but not limited to: application of carbohydrate-rich liquids mainly via nasogastric-tube or gastric infusions, carbohydrate fortification of other feeds (including oral), diazoxide treatment, and somatostatin analogues (e.g., octreotide, octreotide LAR, or lanreotide). Other CHI-specific treatment, either prior to patient's enrolment or during their participation in the trial, could be added upon discussion with the medical monitor.
In Treatment Period 2 (Weeks 5 to 8), all patients received standard of care + dasiglucagon for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Dasiglucagon
Investigational medicinal product code	ZP4207
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Subcutaneous use

Dosage and administration details:

Dosing of dasiglucagon was via an infusion pump with small doses at frequent intervals to approximate continuous infusion. Dasiglucagon injection 4 mg/mL was supplied in a 3 mL vial containing 1 mL, at a concentration of 4 mg/mL. A 2-hour dose-adjustment interval allowed plasma drug levels to approach approximately steady state before the dose was further increased. The maximum cumulative dose over the first 24 hours was 1.26 mg.

Arm title	SofC (Period 1), Dasiglucagon + SoC (Period 2)

Arm description:

In Treatment Period 1 (Weeks 1 to 4), patients in this arm received standard of care for 4 weeks. Standard of care treatment could include most drugs commonly used and/or recommended in treatment of congenital hyperinsulinism (CHI) including, but not limited to: application of carbohydrate-rich liquids mainly via nasogastric-tube or gastric infusions, carbohydrate fortification of other feeds (including oral), diazoxide treatment, and somatostatin analogues (e.g., octreotide, octreotide LAR, or lanreotide). Other CHI-specific treatment, either prior to patient's enrolment or during their participation in the trial, could be added upon discussion with the medical monitor.
In Treatment Period 2 (Weeks 5 to 8), all patients received standard of care + dasiglucagon for 4 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)
Started	16	16
Entered treatment period 2	16	16
Completed	16	15
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Dasiglucagon + standard of care

Reporting group description:

In Treatment Period 1 (Weeks 1 to 4), patients in this arm received standard of care + dasiglucagon for 4 weeks. Standard of care treatment could include most drugs commonly used and/or recommended in treatment of congenital hyperinsulinism (CHI) including, but not limited to: application of carbohydrate-rich liquids mainly via nasogastric-tube or gastric infusions, carbohydrate fortification of other feeds (including oral), diazoxide treatment, and somatostatin analogues (e.g., octreotide, octreotide LAR, or lanreotide). Other CHI-specific treatment, either prior to patient's enrolment or during their participation in the trial, could be added upon discussion with the medical monitor.
In Treatment Period 2 (Weeks 5 to 8), all patients received standard of care + dasiglucagon for 4 weeks.

Reporting group title	SofC (Period 1), Dasiglucagon + SoC (Period 2)

Reporting group description:

In Treatment Period 1 (Weeks 1 to 4), patients in this arm received standard of care for 4 weeks. Standard of care treatment could include most drugs commonly used and/or recommended in treatment of congenital hyperinsulinism (CHI) including, but not limited to: application of carbohydrate-rich liquids mainly via nasogastric-tube or gastric infusions, carbohydrate fortification of other feeds (including oral), diazoxide treatment, and somatostatin analogues (e.g., octreotide, octreotide LAR, or lanreotide). Other CHI-specific treatment, either prior to patient's enrolment or during their participation in the trial, could be added upon discussion with the medical monitor.
In Treatment Period 2 (Weeks 5 to 8), all patients received standard of care + dasiglucagon for 4 weeks.

Reporting group values	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)	Total
Number of subjects	16	16	32
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	6	3	9
Children (2-11 years)	10	13	23
Age continuous Units: years			
arithmetic mean	3.55	5.00	
standard deviation	± 2.592	± 2.892	-
Gender categorical Units: Subjects			
Female	6	10	16
Male	10	6	16
Race Units: Subjects			
White	13	9	22
Black or African American	2	1	3
Asian	1	2	3
Other	0	2	2
More than 1 race	0	2	2
Ethnicity Units: Subjects			
Hispanic or Latino	4	0	4
Not Hispanic or Latino	12	16	28

Pancreatectomy Units: Subjects			
Near total (> 95%)	1	3	4
Not Near total (<= 95%)	3	4	7
No Pancreatectomy	12	9	21
Gastrostomy/nasogastric-tube Units: Subjects			
Gastrostomy	9	12	21
Nasogastric-tube	2	1	3
None	5	3	8
Length/height Units: cm			
arithmetic mean	94.76	105.62	
standard deviation	± 18.805	± 20.534	-
Length/height Z-score			
Z-scores (based on the WHO growth charts) were derived using a patient's age and sex.			
Units: ratio			
arithmetic mean	-0.49	-0.35	
standard deviation	± 1.701	± 1.047	-
Weight Units: kg			
arithmetic mean	17.16	22.79	
standard deviation	± 6.974	± 12.688	-
Weight Z-score			
Z-scores (based on the WHO growth charts) were derived using a patient's age and sex.			
Units: ratio			
arithmetic mean	0.74	0.82	
standard deviation	± 1.725	± 1.412	-

End points

End points reporting groups

Reporting group title	Dasiglucagon + standard of care

Reporting group description:

In Treatment Period 1 (Weeks 1 to 4), patients in this arm received standard of care + dasiglucagon for 4 weeks. Standard of care treatment could include most drugs commonly used and/or recommended in treatment of congenital hyperinsulinism (CHI) including, but not limited to: application of carbohydrate-rich liquids mainly via nasogastric-tube or gastric infusions, carbohydrate fortification of other feeds (including oral), diazoxide treatment, and somatostatin analogues (e.g., octreotide, octreotide LAR, or lanreotide). Other CHI-specific treatment, either prior to patient's enrolment or during their participation in the trial, could be added upon discussion with the medical monitor.
In Treatment Period 2 (Weeks 5 to 8), all patients received standard of care + dasiglucagon for 4 weeks.

Reporting group title	SofC (Period 1), Dasiglucagon + SoC (Period 2)

Reporting group description:

In Treatment Period 1 (Weeks 1 to 4), patients in this arm received standard of care for 4 weeks. Standard of care treatment could include most drugs commonly used and/or recommended in treatment of congenital hyperinsulinism (CHI) including, but not limited to: application of carbohydrate-rich liquids mainly via nasogastric-tube or gastric infusions, carbohydrate fortification of other feeds (including oral), diazoxide treatment, and somatostatin analogues (e.g., octreotide, octreotide LAR, or lanreotide). Other CHI-specific treatment, either prior to patient's enrolment or during their participation in the trial, could be added upon discussion with the medical monitor.
In Treatment Period 2 (Weeks 5 to 8), all patients received standard of care + dasiglucagon for 4 weeks.

Primary: Hypoglycaemia episode rate

End point title	Hypoglycaemia episode rate

End point description:

Hypoglycaemia episode rate was defined as average weekly number of hypoglycaemic episodes (PG <70 mg/dL or 3.9 mmol/L) during Weeks 2-4, as detected by self-monitored plasma glucose (SMPG)

End point type	Primary

End point timeframe:

Weeks 2-4

End point values	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Average weekly episode rate				
arithmetic mean (standard deviation)				
Observed mean values	5.29 (± 5.256)	5.85 (± 2.767)		
Change from baseline	-3.05 (± 4.343)	-3.15 (± 4.753)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary analysis was performed as negative binominal regression analysis comparing the SMPG-detected hypoglycaemia episode rate between treatment groups over weeks 2-4.

Comparison groups	Dasiglucagon + standard of care v SofC (Period 1), Dasiglucagon + SoC (Period 2)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5028
Method	Generalised linear regression
Parameter estimate	Mean difference (net)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.36

Secondary: Fasting tolerance

End point title	Fasting tolerance

End point description:

Fasting tolerance was defined as time from beginning of meal to the first continuous 15-minute continuous glucose monitoring (CGM) reading <70 mg/dL, or the time the test ended if a continuous 15-minute CGM reading <70 mg/dL was not reached.
A number of procedural issues with the test precluded a meaningful interpretation of the results.

End point type	Secondary

End point timeframe:

Weeks 2-4

End point values	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	16		
Units: hours				
arithmetic mean (standard deviation)				
Observed mean values	6.13 (± 5.335)	4.22 (± 4.222)		
Change from baseline	1.20 (± 5.908)	1.27 (± 3.836)		

Statistical analyses

Statistical analysis title	Fasting tolerance

Statistical analysis description:

Increase in fasting tolerance (i.e., change from baseline in time from meal to plasma glucose <70

mg/dL) was analyzed using an ANCOVA, with treatment group and region as fixed effects and baseline fasting tolerance as a covariate.

Comparison groups	Dasiglucagon + standard of care v SofC (Period 1), Dasiglucagon + SoC (Period 2)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6433
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	4.39

Secondary: CGM percent time in range

End point title	CGM percent time in range

End point description:

The continuous glucose monitoring (CGM) percent time in range 70-180 mg/dL (3.9-10.0 mmol/L) during weeks 2-4 was analysed.

End point type	Secondary

End point timeframe:

Weeks 2-4

End point values	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[1]	16		
Units: Average weekly percent time in range				
arithmetic mean (standard deviation)				
Observed mean value	75.10 (± 11.821)	72.65 (± 7.313)		
Change from baseline	-0.97 (± 11.837)	2.44 (± 9.584)		

Notes:

[1] - Change from baseline was analysed for 15 subjects

Statistical analyses

Statistical analysis title	CGM percent time in range

Statistical analysis description:

Percent time in range (i.e., the percent time between 70 mg/dL [3.9 mmol] and 180 mg/dL [10.0 mmol], inclusive), as measured by CGM, was analyzed by using an ANCOVA, with treatment group and region as fixed effects and baseline time in range as a covariate.

Comparison groups	Dasiglucagon + standard of care v SofC (Period 1), Dasiglucagon + SoC (Period 2)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9653
Method	ANCOVA
Parameter estimate	Least-square means
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.48
upper limit	6.78

Secondary: Clinically significant SMPG-detected hypoglycaemia episodes

End point title	Clinically significant SMPG-detected hypoglycaemia episodes
End point description:	
The clinically significant self-monitored plasma glucose (SMPG)-detected hypoglycaemia episodes (PG <54 mg/dL) were analysed.	
End point type	Secondary
End point timeframe:	
Weeks 2-4	

End point values	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Average weekly number of episodes				
arithmetic mean (standard deviation)				
Observed mean values	1.77 (± 1.857)	1.90 (± 1.407)		
Change from baseline	-0.51 (± 2.798)	-0.35 (± 1.446)		

Statistical analyses

Statistical analysis title	Clinically significant hypoglycaemia
Statistical analysis description:	
Analysis of SMPG-detected clinically significant hypoglycaemia (<54 mg/dL [3.0 mmol/L]) episode rate was based on the hypoglycaemia episodes reported with at least 1 SMPG measurement <54 mg/dL. The endpoint was analyzed using a negative binomial regression, with treatment group and region as fixed effects and baseline hypoglycemia rate as a covariate.	
Comparison groups	Dasiglucagon + standard of care v SofC (Period 1), Dasiglucagon + SoC (Period 2)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8114
Method	Negative binomial regression
Parameter estimate	Event rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.74

Secondary: Total amount of gastric carbohydrates administered per week

End point title	Total amount of gastric carbohydrates administered per week

End point description:

Total amount of gastric carbohydrates administered (via nasogastric-tube or gastrostomy) per week to treat hypoglycaemia during weeks 2-4.

End point type	Secondary

End point timeframe:

Weeks 2-4

End point values	Dasiglucagon + standard of care	SofC (Period 1), Dasiglucagon + SoC (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	13		
Units: Grams				
arithmetic mean (standard deviation)				
Observed mean values	22.89 (± 31.415)	37.66 (± 57.998)		
Change from baseline	-33.66 (± 82.767)	-19.74 (± 64.082)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
4 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Dasiglucagon + standard of care (Treatment Period 1)
Reporting group description:	
In Treatment Period 1, patients received standard of care + dasiglucagon or standard of care only for 4 weeks based on their treatment assignment.	
Reporting group title	Standard of care only (Treatment Period 1)
Reporting group description:	
In Treatment Period 1, patients received standard of care + dasiglucagon or standard of care only for 4 weeks based on their treatment assignment.	
Reporting group title	Dasiglucagon + standard of care (Treatment Period 2)
Reporting group description:	
In Treatment Period 2, all patients received standard of care + dasiglucagon for 4 weeks.	
Reporting group title	Dasiglucagon + standard of care (Treatment Periods 1 + 2)
Reporting group description:	
Dasiglucagon + standard of care treatment groups for Treatment Periods 1 and 2. Events reported in the standard of care only group during Treatment Period 1 are not included.	

Serious adverse events	Dasiglucagon + standard of care (Treatment Period 1)	Standard of care only (Treatment Period 1)	Dasiglucagon + standard of care (Treatment Period 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	1 / 16 (6.25%)	2 / 32 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Localised infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Folliculitis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dasiglucagon + standard of care (Treatment Periods 1 + 2)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Localised infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Folliculitis			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dasiglucagon + standard of care (Treatment Period 1)	Standard of care only (Treatment Period 1)	Dasiglucagon + standard of care (Treatment Period 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)	8 / 16 (50.00%)	24 / 32 (75.00%)
General disorders and administration site conditions			
Medical device site irritation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	0	1	0

Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 32 (3.13%)
occurrences (all)	2	1	1
Drooling			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Loss of consciousness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Eye disorders			

Eye movement disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 16 (31.25%)	1 / 16 (6.25%)	2 / 32 (6.25%)
occurrences (all)	7	1	5
Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	2	1	0
Teething			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	1
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	5 / 16 (31.25%)	0 / 16 (0.00%)	1 / 32 (3.13%)
occurrences (all)	5	0	1
Rash			
subjects affected / exposed	3 / 16 (18.75%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	4	0	2
Rash maculo-papular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	2
Dermatitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Miliaria			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Necrolytic migratory erythema			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Localised infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Candida nappy rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gastritis viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Herpangina			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0

Influenza			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 32 (3.13%)
occurrences (all)	0	1	2
Gastroenteritis Viral			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Eczema infected			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	4 / 32 (12.50%)
occurrences (all)	0	0	16
Ketosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2

Non-serious adverse events	Dasiglucagon + standard of care (Treatment Periods 1 + 2)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 32 (84.38%)		
General disorders and administration site conditions			
Medical device site irritation			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 0 / 32 (0.00%) 0		
Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1		
Investigations Hepatic enzyme increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1 2 / 32 (6.25%) 2		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	 2 / 32 (6.25%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Drooling subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all) Loss of consciousness subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 3 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1 0 / 32 (0.00%) 0		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Eye disorders Eye movement disorder subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	7 / 32 (21.88%) 12 2 / 32 (6.25%) 2 2 / 32 (6.25%) 2 1 / 32 (3.13%) 3 1 / 32 (3.13%) 1		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	6 / 32 (18.75%) 6 5 / 32 (15.63%) 6 3 / 32 (9.38%) 3		

Dermatitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Miliaria			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Necrolytic migratory erythema			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Localised infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Candida nappy rash			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Gastritis viral			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Herpangina			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Gastroenteritis Viral			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Eczema infected			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	16		
Ketosis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2019	Amendment 5 (Germany). Device adapted protocol to fulfil the requirements from BfArM MPG. New section 19 added + additional device-related safety reporting added in section 11.
03 June 2019	Amendment 6 (all countries, except Germany). Main changes: Primary analysis changed (FDA request). Endpoints aligned to trial ZP4207-17103. Clarifications to hypoglycaemia reporting and electronic SMPG data. Clarified that standard of care open-label CGM is not allowed. Immunogenicity strategy updated.
05 July 2019	Amendment 7 (Germany). Local German protocol combining protocol versions 6.0 and 7.0.
19 September 2019	Amendment 8 (all countries, except Germany). Additional electrocardiogram and vital signs assessments (FDA request). Immunogenicity strategy updated (FDA).
11 October 2019	Amendment 9 (Germany). Local German protocol combining protocol versions 8.0 and 9.0.
06 March 2020	Amendment 10 (all countries, except Germany). Interim analyses removed. Immunogenicity section updated.
11 March 2020	Amendment 11 (Germany). Local German protocol combining protocol version 10.0 and changes according to protocol version 11.0.
05 October 2020	Amendment 12 (all countries, except Germany). Second key secondary efficacy endpoint related to assessment of gastric carbohydrates moved to be a secondary efficacy endpoint. All endpoints related to intake of gastric carbohydrates only to be described in the subgroup of patients who have a gastrostomy/nasogastric-tube at screening. Amendment finalized 12-Nov-2020, after LPLV but prior to DBL.
05 October 2020	Amendment 13 (Germany). Local German protocol combining protocol versions 12.0 and 13.0. Amendment finalized 12-Nov-2020, after LPLV but prior to DBL.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported