Clinical trial results:
An Open-Label Multiple-Dose Study of RZ358 in Patients with Congenital Hyperinsulinism

Summary

EudraCT number	2016-004186-83
Trial protocol	GB DE DK BG ES
Global end of trial date	14 June 2022

Results information

Result version number	v1 (current)
This version publication date	01 December 2023
First version publication date	01 December 2023

Trial information

Trial identification

Sponsor protocol code	RZ358-606

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04538989
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 119319

Notes:

Sponsors

Sponsor organisation name	Rezolute, Inc
Sponsor organisation address	275 Shoreline Drive, Suite 500, Redwood City, United States, CA 94065
Public contact	Clinical Trials Info, Rezolute, Inc, +1 650206-4507, info@rezolutebio.com
Scientific contact	Clinical Trials Info, Rezolute, Inc, +1 650206-4507, info@rezolutebio.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	19 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2022
Global end of trial reached?	Yes
Global end of trial date	14 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and glycemic efficacy of multiple ascending doses of RZ358 administered for 8 weeks in patients with hyperinsulinemic hypoglycemia due to congenital hyperinsulinism (CHI).

Protection of trial subjects:

Children represented the primary target population for RZ358 and younger patients with CHI tend to have the most severe disease and most significant unmet need, so it was desirable and necessary to conduct the clinical trial in younger-age children to fully understand the efficacy and safety in this population. The combined non-clinical and clinical PK, PD, and safety data available supported a good benefit-to-risk rationale for conducting the study in adults and children aged 2 and above.
Protection and safety of children was ensured (including minimisation of risks and burden) through use of appropriately trained staff and paediatric experts available at the trial sites. Furthermore, during the development of the RZ358-606 protocol, patients and families from the patient advocacy group Congenital Hyperinsulinism International were involved in the design of the study to ensure that the patient and parent perspectives were taken into consideration. The main aims of their involvement were to minimise risk and burden for participants and their families.
At any sign of distress the trial procedure could be stopped; and time allowed for the child to feel in control and to allow further age appropriate explanation. Assessments were made on an ongoing basis to continue or abandon the procedure if the child remained distressed, or even withdraw the child from the trial.

Background therapy:

The trial design was an add-on to existing therapies (diazoxide, lanreotide, sirolimus, pasireotide, or octreotide and/or nutritional supplementation) when those therapies had substantially failed the patient and they had significant residual hypoglycemia, whether or not they adequately tolerated those same therapies.

Evidence for comparator:

Not applicable, no comparators used in this study.

Actual start date of recruitment	24 February 2020
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	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Israel: 1

Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	23
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)	0
Children (2-11 years)	19
Adolescents (12-17 years)	3
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began on 24 February 2020 and finished on 13 Jan 2022. Participants were recruited from Bulgaria, Canada, Denmark, Germany, Spain, UK, Georgia, Israel, Turkey, Russia and the USA.

Pre-assignment

Screening details:

There was a 10 day CGM and gylcemic eligibility evaluation as part of the screening. Those who experienced glucose values <70 mg/dL (3.9 mmol/L) for ≥4% of the overall monitored CGM time with at least 3 severe hypoglycemia events by CGM threshold of <50 mg/dL (2.8 mmol/L) during the last 7 days of evaluation period were eligible per this criteria

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	RZ358-606 Cohort 1_Overall

Arm description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Arm type	Experimental
Investigational medicinal product name	RZ358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the 8 week treatment period patients in this cohort received RZ358 3mg/kg as an IV infusion over 30 minutes every two weeks. No treatment was received during the baseline or follow-up periods.

Arm title	RZ358-606 Cohort 2_Overall

Arm description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Arm type	Experimental
Investigational medicinal product name	RZ358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the 8 week treatment period patients in this cohort received RZ358 6mg/kg as an IV infusion over 30 minutes every two weeks. No treatment was received during the baseline or follow-up periods.

Arm title	RZ358-606 Cohort 3_Overall

Arm description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Arm type	Experimental
Investigational medicinal product name	RZ358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the 8 week treatment period patients in this cohort received RZ358 9mg/kg as an IV infusion over 30 minutes every two weeks. No treatment was received during the baseline or follow-up periods.

Arm title	RZ358-606 Cohort 4_Overall

Arm description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Arm type	Experimental
Investigational medicinal product name	RZ358
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the 8 week treatment period, patients in this cohort received RZ358as an IV infusion over 30 minutes every two weeks (bi-weekly fixed dose-titration from 3 to 9 mg/kg for the first 4 weeks, followed by a fixed 9 mg/kg dose amount thereafter for the remaining 4 weeks). No treatment was received during the baseline or follow-up periods.

Number of subjects in period 1	RZ358-606 Cohort 1_Overall	RZ358-606 Cohort 2_Overall	RZ358-606 Cohort 3_Overall
Started	4	8	8
Completed	4	8	8

Number of subjects in period 1	RZ358-606 Cohort 4_Overall
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	23	23	
Age categorical			
All subjects were age 2-64 years			
Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	19	19	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	1	1	
Age continuous			
Units: years			
arithmetic mean	6.7		
standard deviation	± 5.50	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	13	13	
Standard of Care Treatment at Study Entry			
Units: Subjects			
Diazoxide	6	6	
Somatostatin Analogs	8	8	
Somatostatin Analogs and Continuous Enteral Nutrit	3	3	
Somatostatin Analogs and Sirolimus	1	1	
Diazoxide and Continuous Enteral Nutrition	1	1	
Pancreatectomy	3	3	
Diazoxide and Pancreatectomy	1	1	

End points

End points reporting groups

Reporting group title	RZ358-606 Cohort 1_Overall

Reporting group description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Reporting group title	RZ358-606 Cohort 2_Overall

Reporting group description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Reporting group title	RZ358-606 Cohort 3_Overall

Reporting group description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Reporting group title	RZ358-606 Cohort 4_Overall

Reporting group description:

Includes baseline, treatment, and follow-up periods. Baseline is defined as the last non-missing value. For aggregate/integrated glycemic endpoints by SMBG or CGM, Baseline was defined as the cumulative ≥ 10-day period of SMBG or CGM measurement preceding the first dose, and the on-treatment efficacy evaluable period (8 weeks) was defined as the cumulative 2-week period of SMBG and CGM measurement following the last dose of RZ358.

Subject analysis set title	Per Protocol_Baseline_Cohort 1
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Baseline_Cohort 2
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Baseline_Cohort 3
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Baseline_Cohort 4
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

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

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Treatment_Cohort 1
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Treatment_Cohort 2
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Treatment_Cohort 3
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Treatment_Cohort 4
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

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

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Change from Baseline_Cohort 1
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol

deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Change from Baseline_Cohort 2
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Change from Baseline_Cohort 3
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Change from Baseline_Cohort 4
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	Per Protocol_Change from Baseline_Total
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who received at least 4 Wks of study drug (2 bi-weekly doses), with no major protocol violations. A patient in the Per protocol population was excluded from one or more specific efficacy analyses (i.e., SMBG-related endpoints or CGM-related endpoints), if they had a major protocol deviation affecting only that endpoint (e.g., non-compliance with SMBG only, or non-compliance with CGM only).

Subject analysis set title	PK population_Cohort 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received study drug and have a sufficient number and quality (biologically plausible) of results.

Subject analysis set title	PK population_Cohort 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received study drug and have a sufficient number and quality (biologically plausible) of results.

Subject analysis set title	PK population_Cohort 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received study drug and have a sufficient number and quality (biologically plausible) of results.

Subject analysis set title	PK population_Cohort 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received study drug and have a sufficient number and quality (biologically plausible) of results.

Primary: The glycemic efficacy of RZ358 as evaluated by the average daily percent time within a glucose target range of 70-180 mg/dL (3.9-10 mmol/L) by CGM.

End point title	The glycemic efficacy of RZ358 as evaluated by the average daily percent time within a glucose target range of 70-180 mg/dL (3.9-10 mmol/L) by CGM.[1]

End point description:

This was not a powered study; thus, the primary and key, clinically-relevant secondary efficacy endpoints are interchangeable from a statistical perspective and should be interpreted accordingly, for this proof-of-concept study.

Time in range, 70-180 mg/dL, was also assessed by CGM. Across all doses, there was an improvement in time spent in range by 8%. A response of 16% was observed at the highest dose and a more pronounced response of >25% was observed in patients without baseline hyperglycemia on SOC. RZ358's ability to increase time and range spent in normoglycemia by >25% in patients who were not on background therapies without hyperglycemia further establishes its potential as a monotherapy for congenital HI

End point type	Primary

End point timeframe:

Baseline and end of treatment. EOT is defined as the period of the final dose plus 14 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistics for this endpoint cannot be correctly reported due to the limitations of this system.

End point values	Per Protocol_Baseline_Cohort 1	Per Protocol_Baseline_Cohort 2	Per Protocol_Baseline_Cohort 3	Per Protocol_Baseline_Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	8	7	3
Units: percent				
arithmetic mean (standard deviation)	81.528 (± 6.916)	74.221 (± 8.028)	68.997 (± 27.894)	67.643 (± 16.898)

End point values	Per Protocol_Baseline_Total	Per Protocol_Treatment_Cohort 1	Per Protocol_Treatment_Cohort 2	Per Protocol_Treatment_Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	4	8	7
Units: percent				
arithmetic mean (standard deviation)	72.990 (± 17.369)	85.958 (± 8.994)	74.839 (± 16.420)	79.367 (± 13.247)

End point values	Per Protocol_Treatment_Cohort 4	Per Protocol_Treatment_Total	Per Protocol_Change from Baseline_Cohort 1	Per Protocol_Change from Baseline_Cohort 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	22	4	8
Units: percent				
arithmetic mean (standard deviation)	72.433 (± 8.661)	77.973 (± 13.402)	4.430 (± 4.222)	0.618 (± 19.491)

End point values	Per Protocol_Change from Baseline_Cohort 3	Per Protocol_Change from Baseline_Cohort 4	Per Protocol_Change from Baseline_Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	3	22	
Units: percent				
arithmetic mean (standard deviation)	10.370 (± 21.777)	4.790 (± 9.818)	4.983 (± 17.054)	

Statistical analyses

No statistical analyses for this end point

Primary: Repeat-dose PK of RZ358

End point title	Repeat-dose PK of RZ358[2]

End point description:

All patients who received RZ358 and for whom the primary PK data was considered to be sufficient and interpretable were to be included in the PK analyses. Individual and mean plasma concentration data is summarized descriptively at the specified timepoints. The results of this study may be combined with those of other studies for analysis and modeling (e.g., population PK and PK-PD), and therefore the PK parameters are reported separately, as part of an iterative population PK approach.

End point type	Primary

End point timeframe:

From pre-dose and 1 h after the start of infusion on each dosing day, 24 h post-dose on Day 2 of each dosing Wk, 48 h post-dose on Day 3 (Wk 1 only), and at outpatient follow-up visits.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The results of this study may be combined with those of other studies for analysis and modeling (e.g.,population PK and PK-PD), and therefore the PK parameters are reported separately, as part of an iterative population PK approach

End point values	PK population_Cohort 1	PK population_Cohort 2	PK population_Cohort 3	PK population_Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4[3]	8[4]	8[5]	3[6]
Units: Concentration µg/mL				
geometric mean (standard deviation)				
pre Wk1 dose	0 (± 0)	0 (± 0)	55648 (± 0)	0 (± 0)
1 hr post Wk1/D1 dose	29093 (± 43188)	120368 (± 36668)	164047 (± 54035)	43593 (± 8835)
pre Wk3 dose	38951 (± 28296)	28397 (± 5936)	41512 (± 13015)	8961 (± 1703)
pre Wk5 dose	20692 (± 0)	82646 (± 120416)	74457 (± 15208)	34243 (± 8130)
pre Wk7 dose	31902 (± 0)	56919 (± 18798)	95721 (± 22293)	55532 (± 10717)

1hr post Wk7 dose	94593 (± 0)	178090 (± 47312)	280843 (± 131841)	245905 (± 144257)
FU Day 14/EOT	59542 (± 17383)	70990 (± 16506)	105005 (± 19779)	110134 (± 17019)
FU Day 28	46751 (± 45750)	39385 (± 10560)	63201 (± 19423)	52039 (± 5015)
FU Day 42	23166 (± 6686)	24226 (± 24226)	43034 (± 11961)	37394 (± 10540)
FU Day 105	2307 (± 953)	4231 (± 5508)	9269 (± 3944)	4194 (± 1786)

Notes:

[3] - At pre Wk1, Wk5 and Wk7 dose, only data for 1 patient is available, hence SD is entered as 0

[4] - No patients analysed at preWk1 dose and on FU Day 28 7pts analysed.

[5] - 1 patient analysed at preWk1 dose and 7 patients at 1hr post dose Wk1, preWk3, FU Day 14 &105

[6] - No patients analysed at preWk1 dose, hence mean & SD is entered as 0

Statistical analyses

No statistical analyses for this end point

Secondary: Average weekly incidence of hypoglycemia (< 70 mg/dL) by self-monitored blood glucose (SMBG)

End point title	Average weekly incidence of hypoglycemia (< 70 mg/dL) by self-monitored blood glucose (SMBG)

End point description:

This was not a powered study; thus, the primary and key, clinically-relevant secondary efficacy endpoints are interchangeable from a statistical perspective and should be interpreted accordingly, for this proof-of-concept study. Significant and generally dose-dependent improvements from baseline in total (<70 mg/dL) hypoglycemia events were observed by BGM, with a mean improvement of approximately 50-70% (p ≤0.01) for the pooled RZ358 treated subjects across all doses.

End point type	Secondary

End point timeframe:

Baseline and end of treatment. EOT is defined as the period of the final dose plus 14 days.

End point values	Per Protocol_Baseline_Cohort 1	Per Protocol_Baseline_Cohort 2	Per Protocol_Baseline_Cohort 3	Per Protocol_Baseline_Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	8	7	2
Units: average events per week				
arithmetic mean (standard deviation)	10.070 (± 3.065)	15.939 (± 15.554)	16.181 (± 7.609)	9.295 (± 1.704)

End point values	Per Protocol_Baseline_Total	Per Protocol_Treatment_Cohort 1	Per Protocol_Treatment_Cohort 2	Per Protocol_Treatment_Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	3	8	7
Units: average events per week				
arithmetic mean (standard deviation)	14.479 (± 10.790)	8.640 (± 2.735)	8.999 (± 7.891)	5.057 (± 8.388)

End point values	Per Protocol_Treatment_Cohort 4	Per Protocol_Treatment_Total	Per Protocol_Change from Baseline_Cohort 1	Per Protocol_Change from Baseline_Cohort 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	20	3	8
Units: average events per week				
arithmetic mean (standard deviation)	7.595 (± 2.963)	7.425 (± 7.053)	-1.430 (± 5.673)	-6.940 (± 10.126)

End point values	Per Protocol_Change from Baseline_Cohort 3	Per Protocol_Change from Baseline_Cohort 4	Per Protocol_Change from Baseline_Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	2	20	
Units: average events per week				
arithmetic mean (standard deviation)	-11.124 (± 5.500)	-1.700 (± 1.259)	-7.054 (± 8.057)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average daily percent time with hypoglycemia at threshold of <70mg/dL (3.9 mmol/L) by continuous glucose monitoring

End point title	Average daily percent time with hypoglycemia at threshold of <70mg/dL (3.9 mmol/L) by continuous glucose monitoring

End point description:

This was not a powered study; thus, the primary and key, clinically-relevant secondary efficacy endpoints are interchangeable from a statistical perspective and should be interpreted accordingly, for this proof-of-concept study.

Improvements in duration of hypoglycemia by CGM were comparable to the observed reductions in hypoglycemia events by BGM. There was a ≥25% reduction in average daily percent time with hypoglycemia by CGM at the threshold of <70mg/dL by CGM across all dosing cohorts. Cohorts 2 and 3 experienced decreases from baseline in average daily percent time spent in hypoglycemia of 59% ($p<0.01$) and 65%, respectively. The difference in magnitude of improvement of hypoglycemia among cohorts elucidates a clear dose-response relationship.

End point type	Secondary

End point timeframe:

Baseline and end of treatment. EOT is defined as the period of the final dose plus 14 days

End point values	Per Protocol_Baseline_Cohort 1	Per Protocol_Baseline_Cohort 2	Per Protocol_Baseline_Cohort 3	Per Protocol_Baseline_Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	8	7	3
Units: percent				
arithmetic mean (standard deviation)	16.338 (± 5.345)	21.675 (± 8.821)	26.281 (± 29.684)	29.213 (± 16.351)

End point values	Per Protocol_Baseline_Total	Per Protocol_Treatment_Cohort 1	Per Protocol_Treatment_Cohort 2	Per Protocol_Treatment_Cohort 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	4	8	7
Units: percent				
arithmetic mean (standard deviation)	23.198 (± 18.039)	10.425 (± 5.745)	9.533 (± 7.760)	9.649 (± 11.838)

End point values	Per Protocol_Treatment_Cohort 4	Per Protocol_Treatment_Total	Per Protocol_Change from Baseline_Cohort 1	Per Protocol_Change from Baseline_Cohort 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	22	4	8
Units: percent				
arithmetic mean (standard deviation)	16.273 (± 9.127)	10.651 (± 8.837)	-5.913 (± 3.003)	-12.143 (± 10.136)

End point values	Per Protocol_Change from Baseline_Cohort 3	Per Protocol_Change from Baseline_Cohort 4	Per Protocol_Change from Baseline_Total	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	3	22	
Units: percent				
arithmetic mean (standard deviation)	-16.633 (± 20.893)	-12.940 (± 7.380)	-12.547 (± 13.397)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported from the time of informed consent for participation in the study until the end of study visit.

Adverse event reporting additional description:

A total of 41 TEAEs occurred in 16 subjects over the evaluation period, compared to a total of 17 non-TEAEs in 10 subjects that occurred over the ~1 month pre-treatment period. Therefore, on a time-adjusted basis, there was no significant difference in the number of AEs during RZ358 treatment compared to pre-treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Cohort 1_Safety Population

Reporting group description:

Cohort 1, 3mg/kg

Reporting group title	Cohort 2_Safety Population

Reporting group description:

Cohort 2, 6mg/kg

Reporting group title	Cohort 3_Safety Population

Reporting group description:

Cohort 3, 9mg/kg

Reporting group title	Cohort 4_Safety Population

Reporting group description:

Bi-weekly fixed dose-titration from 3 to 9 mg/kg for the first 4 weeks, followed by a fixed 9 mg/kg dose amount thereafter for the remaining 4 weeks

Reporting group title	Non-TEAE_Safety Population

Reporting group description:

AEs that occurred pre-treatment and after 42 days post treatment

Serious adverse events	Cohort 1_Safety Population	Cohort 2_Safety Population	Cohort 3_Safety Population
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (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

Serious adverse events	Cohort 4_Safety Population	Non-TEAE_Safety Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1_Safety Population	Cohort 2_Safety Population	Cohort 3_Safety Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	7 / 8 (87.50%)	5 / 8 (62.50%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infusion site reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Medical device pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Contusion			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Chalazion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Acanthosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hypertrichosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Sacral pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort 4_Safety Population	Non-TEAE_Safety Population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	10 / 23 (43.48%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Infusion site reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Medical device pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Respiratory disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Generalised tonic-clonic seizure			

subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Presyncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			

subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Acanthosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Dermatitis contact			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Dermatitis atopic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Hypertrichosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Sacral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	1	

Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 3 (0.00%)	0 / 23 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2016	Amendment 1 - protocol version not implemented and no patients were recruited under this version
10 May 2017	Amendment 2 - protocol version not implemented and no patients were recruited under this version
12 August 2019	Amendment 3 - Protocol version implemented for patient recruitment (1 patient enrolled)
19 May 2020	Amendment 4 - The Protocol inclusion criteria and endpoints were amended slightly
17 March 2021	Amendment 5 - The dosing frequency and visit schedule were reduced

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: