Clinical trial results:
Original: An Open-Label, Long-Term Safety and Efficacy Evaluation of Diazoxide Choline Extended-Release Tablets in Participants with Prader-Willi Syndrome

Amendment 3: An Open-Label, Long-Term Safety and Efficacy Evaluation of Diazoxide Choline Controlled-Release Tablet in Patients with Prader-Willi Syndrome

Amendment 7: An Open-Label, Long-Term Safety and Efficacy Evaluation of Diazoxide Choline Extended-Release Tablets in Participants with Prader-Willi Syndrome with a Double-Blind, Placebo-Controlled, Randomized Withdrawal Period

Summary

EudraCT number	2018-004216-22
Trial protocol	GB
Global end of trial date	28 February 2024

Results information

Result version number	v1 (current)
This version publication date	02 September 2024
First version publication date	02 September 2024

Trial information

Trial identification

Sponsor protocol code	C602

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03714373
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Soleno Therapeutics UK Limited
Sponsor organisation address	Garden Cottage, Badgemore Park, Henley-on Thames, United Kingdom, RG9 4NR
Public contact	Clinical Trial Information, Soleno Therapeutics UK Limited, +44 1628876432, soleno-uk@soleno.life
Scientific contact	Clinical Trial Information, Soleno Therapeutics UK Limited, +44 16288756023, C602ProjectManager@soleno.life

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	28 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2024
Global end of trial reached?	Yes
Global end of trial date	28 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Open Label Extension (OLE) Period: to evaluate the long-term safety of DCCR (diazoxide choline) extended-release tablets in participants with Prader-Willi syndrome (PWS) previously enrolled in clinical study C601.

Randomized Withdrawal (RW) Period: to evaluate the effects of discontinuation of treatment with DCCR (diazoxide choline) extended-release tablets and initiation of placebo compared to continued treatment with DCCR in participants with Prader-Willi syndrome (PWS) on hyperphagia as assessed by change in the hyperphagia questionnaire for clinical trials (HQ-CT) Total Score from RW Period Baseline at RW Week 16.

Protection of trial subjects:

IDMC (Independent Data Monitoring Committee) met 3 times during the RW Period to review unblinded safety data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 91
Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	115
EEA total number of subjects	0

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)	55
Adolescents (12-17 years)	39
Adults (18-64 years)	21
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

C602 OLE (Period 1): People who completed C601 were given the option to enrol. The first subject was screened in the US on 17May18 & in the UK on 26Jun19; all sites were either hospitals or academic medical centres.
C602 RW (Period 2): People who participated in C602 OLE & completed the OLE EOT Visit procedures were given the option to enrol.

Pre-assignment

Screening details:

C602 OLE (Period 1): 120 participants were eligible and 115 participants enrolled and took any amount of study drug.

C602 RW (Period 2): 83 participants were eligible and 77 participants enrolled and took any amount of study drug.

Period 1

Period 1 title	Open-Label Extension Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

To maintain the blinded treatment assignment in clinical study C601, dosing remained blinded during the titration period of clinical study C602.

Arms

Arm title	DCCR (Open-Label)

Arm description:

Once daily oral administration of open-label study medication.

Arm type	Open-Label
Investigational medicinal product name	DCCR
Investigational medicinal product code	
Other name	Diazoxide choline controlled release, Diazoxide choline extended-release
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg DCCR tablets could be taken; DCCR was taken once daily. Tablets were to be swallowed whole and not be broken, crushed or chewed.

The target doses by weight(kg) were as follows:

Subjects weighing 20 to <30 kg took 100 mg DCCR/day
Subjects weighing equal to or greater than 30 to <40 kg took 150 mg DCCR/day
Subjects weighing equal to or greater than 40 to <65 kg took 225 mg DCCR/day
Subjects weighing equal to or greater than 65 to <100 kg took 375mg DCCR/day
Subjects weighing equal to or greater than 100 to <135 kg took 450 mg DCCR/day
Subjects were titrated every 2 weeks until the target dose was achieved.

Number of subjects in period 1	DCCR (Open-Label)
Started	115
Completed ≥13 weeks of DCCR treatment	113
Completed at least of DCCR treatment	105
Completed 2 years of DCCR treatment	88
Eligible to enrol in RWP as of Oct 2022	83
Completed	77
Not completed	38
Adverse event, not serious	5
Medication change	1
Perceived lack of effectiveness	5
Consent withdrawn by subject	18
Investigator/Caregiver decision	2
Non-compliance	3
Lost to follow-up	4

Period 2

Period 2 title	Randomised Withdrawal Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study team members were blinded to the randomised assignment. Study drug was also blinded. Placebo tablets matching the size, shape and colour of the respective DCCR tablet strengths were used.

Arms

Are arms mutually exclusive?	Yes
Arm title	DCCR (Double-blind)

Arm description:

Once daily oral administration of double-blind study medication.

Arm type	Experimental
Investigational medicinal product name	DCCR
Investigational medicinal product code	
Other name	Diazoxide choline controlled release, Diazoxide choline extended-release
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg DCCR tablets could be taken; DCCR was taken once daily. Tablets were to be swallowed whole and not be broken, crushed or chewed.

The target doses by weight(kg) were as follows:

Subjects weighing 20 to <30 kg took 100 mg DCCR/day
Subjects weighing equal to or greater than 30 to <40 kg took 150 mg DCCR/day
Subjects weighing equal to or greater than 40 to <65 kg took 225 mg DCCR/day
Subjects weighing equal to or greater than 65 to <100 kg took 375 mg DCCR/day
Subjects weighing equal to or greater than 100 to <135 kg took 450 mg DCCR/day
Subjects were titrated every 2 weeks until the target dose was achieved.

Arm title	Placebo for DCCR (Double-blind)

Arm description:

Once daily oral administration of double-blind study medication.

Arm type	Placebo
Investigational medicinal product name	Placebo for DCCR (Double-blind)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with PWS were dosed dependent on their weight; 25mg, 75mg or 150mg placebo tablets could be taken; Placebo was taken once daily. Tablets were to be swallowed whole and not be broken, crushed or chewed.

The target doses by weight(kg) were as follows:

Subjects weighing 20 to <30 kg took 100 mg placebo/day
Subjects weighing equal to or greater than 30 to <40 kg took 150 mg placebo/day
Subjects weighing equal to or greater than 40 to <65 kg took 225 mg placebo/day
Subjects weighing equal to or greater than 65 to <100 kg took 375 mg placebo/day
Subjects weighing equal to or greater than 100 to <135 kg took 450 mg placebo/day
Subjects randomised to the placebo group were titrated on placebo, similar to the DCCR group.

Number of subjects in period 2	DCCR (Double-blind)	Placebo for DCCR (Double-blind)
Started	38	39
Completed	37	39
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Open-Label Extension Period

Reporting group description:

The reporting group included 115 subjects who were all being treated with DCCR.

Reporting group values	Open-Label Extension Period	Total	
Number of subjects	115	115	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	55	55	
Adolescents (12-17 years)	39	39	
Adults (18-64 years)	21	21	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	12.9		
full range (min-max)	4 to 44	-	
Gender categorical Units: Subjects			
Female	66	66	
Male	49	49	

Subject analysis sets

Subject analysis set title	RW Intent-to-Treat (RWITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The RW Intent-to-Treat Population analysis set includes all participants who were randomised to DCCR or Placebo during the RW Period.

Subject analysis set title	RW Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The RW Safety Population consists of participants who received any amount of study drug during the RW Period.

Subject analysis set title	C602 Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The C602 Safety Population included all participants who received ≥1 dose of DCCR in Study C602 OLE Period.

Reporting group values	RW Intent-to-Treat (RWITT)	RW Safety Population	C602 Safety Population
Number of subjects	77	77	115
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	23	23	55
Adolescents (12-17 years)	31	31	39
Adults (18-64 years)	23	23	21
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	14.9	14.9	12.9
full range (min-max)	7 to 29	7 to 29	4 to 44
Gender categorical Units: Subjects			
Female	43	43	66
Male	34	34	49

End points

End points reporting groups

Reporting group title	DCCR (Open-Label)
Reporting group description:	
Once daily oral administration of open-label study medication.	
Reporting group title	DCCR (Double-blind)
Reporting group description:	
Once daily oral administration of double-blind study medication.	
Reporting group title	Placebo for DCCR (Double-blind)
Reporting group description:	
Once daily oral administration of double-blind study medication.	
Subject analysis set title	RW Intent-to-Treat (RWITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The RW Intent-to-Treat Population analysis set includes all participants who were randomised to DCCR or Placebo during the RW Period.	
Subject analysis set title	RW Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The RW Safety Population consists of participants who received any amount of study drug during the RW Period.	
Subject analysis set title	C602 Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The C602 Safety Population included all participants who received ≥1 dose of DCCR in Study C602 OLE Period.	

Primary: Hyperphagia Questionnaire (HQ-CT) Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point title	Hyperphagia Questionnaire (HQ-CT) Change from Randomised Withdrawal (RW) Period Baseline at Week 16
End point description:	
Hyperphagia-related behaviours were assessed by the validated hyperphagia questionnaire for clinical trials (HQ-CT), an instrument designed to measure symptoms of food related preoccupations and behaviours that was completed by the caregiver. The HQ-CT consists of nine items with responses ranging from 0–4 units each (possible total score range: 0−36). The HQ-CT was assessed at Baseline and at Week 4, Week 8, Week 12, and Week 16. A decrease in score from baseline represented improvement.	
End point type	Primary
End point timeframe:	
RW Period Baseline to Week 16	

End point values	DCCR (Double-blind)	Placebo for DCCR (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: HQ-CT Score				
least squares mean (standard error)	2.6 (± 1.12)	7.6 (± 1.09)		

Statistical analyses

Statistical analysis title	Primary endpoint – Hyperphagia Questionnaire HQ-CT

Statistical analysis description:

The primary endpoint (change from RW Baseline at Week 16 in the HQ-CT score) was analyzed using a linear mixed model for repeated measurements in the RWITT Population. Missing values were not imputed, and data collected after treatment discontinuation were included. LS mean values were based on a mixed model for repeated measures adjusting for RW Baseline HQ-CT score, treatment, visit (RW Weeks 4, 8, 12, and 16), and treatment by visit interaction, using an unstructured covariance matrix.

Comparison groups	DCCR (Double-blind) v Placebo for DCCR (Double-blind)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	-1.8
Variability estimate	Standard error of the mean
Dispersion value	1.57

Secondary: Clinical Global Impression of Severity (CGI-S) Score Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point title	Clinical Global Impression of Severity (CGI-S) Score Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point description:

The CGI-S (1-7) was a single statement designed to assess the Investigator’s overall perception of the severity of the participant’s illness across the course of the clinical trial. The Investigator provided a response to “Considering your total clinical experience with this particular population, how ill is this patient at this time:” by rating the participant’s illness severity using a 7-point response scale: 1=“Normal, not at all ill”, 2=“Borderline ill”, 3=“Mildly ill”, 4=“Moderately ill”, 5=“Markedly ill”, 6=“Severely ill”, and 7=“Among the most extremely ill participants”.

End point type	Secondary

End point timeframe:

RW Period Baseline to Week 16

End point values	DCCR (Double-blind)	Placebo for DCCR (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: CGI-S Score				
least squares mean (standard error)	0.9 (± 0.19)	1.4 (± 0.18)		

Statistical analyses

Statistical analysis title	Secondary endpoint - CGI-S Score

Statistical analysis description:

The secondary endpoint (change from RW Baseline at Week 16 in CGI-S Score) was analysed using a compound symmetry matrix in the repeated measures models. LS mean values are based on a mixed model for repeated measures adjusting for RW Baseline CGI-S score as a continuous covariate, RW Baseline HQ-CT Total Score category (<13 vs. 13-36), treatment, visit (RW Week 4, 8, 12, and 16), and treatment by visit interaction, using an unstructured covariance matrix.

Comparison groups	DCCR (Double-blind) v Placebo for DCCR (Double-blind)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0794
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.24

Secondary: Clinical Global Impression of Improvement (CGI-I) Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point title	Clinical Global Impression of Improvement (CGI-I) Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point description:

The Clinical Global Impression of Improvement (CGI-I) for Improvement is a single statement designed to assess the Investigator's overall perception of change in the subject's condition across the course of the clinical trial. The Investigator provided a response to "Compared to the subject's condition at enrollment, the subject's condition is:" by rating the subject's behavior using a 7-point response scale: 1="Very much improved", 2="Much improved", 3="Minimally improved", 4="No change", 5="Minimally worse", 6="Much worse", and 7="Very much worse". Thirty-six of 38 participants in the DCCR group and 39 of 39 in the Placebo group contributed data at Week 16.

End point type	Secondary

End point timeframe:

RW Period Baseline to Week 16

End point values	DCCR (Double-blind)	Placebo for DCCR (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	39		
Units: Participants				
Other (1-5)	27	21		
Much worse (6) and Very much worse (7)	9	18		

Statistical analyses

Statistical analysis title	Secondary endpoint – CGI-I Score

Statistical analysis description:

Reported common odds ratio (OR) is from a logistic regression proportional-odds model including fixed effects for treatment and adjusted for RW Baseline HQ-CT Total Score category (<13 vs. 13-36), with OR > 1 corresponding to values favouring DCCR. The OR (for Placebo/DCCR) is for the odds of having a higher value for the ordinal category. At Week 16, tail categories 1, 2, 3 and 4 were consolidated, as well as categories 6 and 7, to ensure ≥5 responses in each treatment group and visit/category.

Comparison groups	DCCR (Double-blind) v Placebo for DCCR (Double-blind)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0918
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.887
upper limit	4.929

Other pre-specified: Body Weight Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point title	Body Weight Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point description:

Weight (kg) was collected at RW Baseline and at RW Week 16.

End point type	Other pre-specified

End point timeframe:

RW Period Baseline to Week 16.

End point values	DCCR (Double-blind)	Placebo for DCCR (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Kg				
least squares mean (standard error)	0.8 (± 0.58)	2.4 (± 0.56)		

Statistical analyses

Statistical analysis title	Additional endpoint - Weight
Statistical analysis description:	
Missing values were not imputed, and data collected after treatment discontinuation are included. LS Means are based on an ANCOVA model adjusting for RW baseline weight and RW Baseline HQ-CT Total Score category (<13 versus 13-36).	
Comparison groups	DCCR (Double-blind) v Placebo for DCCR (Double-blind)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0353
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.75

Other pre-specified: Body Mass Index (BMI) Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point title	Body Mass Index (BMI) Change from Randomised Withdrawal (RW) Period Baseline at Week 16
End point description:	
BMI was calculated based on weight and height and was collected at RW Baseline and at RW Week 16 or EOT.	
End point type	Other pre-specified
End point timeframe:	
RW Period Baseline to Week 16.	

End point values	DCCR (Double-blind)	Placebo for DCCR (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Kg/m2				
least squares mean (standard error)	0.2 (± 0.22)	0.8 (± 0.22)		

Statistical analyses

Statistical analysis title	Additional endpoint - Body Mass Index (BMI)

Statistical analysis description:

Missing values are not imputed, and data collected after treatment discontinuation are included. LS Means are based on an ANCOVA model adjusting for RW baseline BMI and RW Baseline HQ-CT Total Score category (<13 versus 13-36).

Comparison groups	DCCR (Double-blind) v Placebo for DCCR (Double-blind)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0336
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.29

Other pre-specified: Body Mass Index (BMI) Z-Score Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point title	Body Mass Index (BMI) Z-Score Change from Randomised Withdrawal (RW) Period Baseline at Week 16

End point description:

BMI Z-Scores were calculated using the Lambda, Mu, and Sigma Method (LMS) method as:

Z = [((BMI / M)**L) – 1] / (S * L). LMS parameters were obtained using BMI for age charts provided by the Centers for Disease Control and Prevention (CDC). The participants age at the time of the assessment was used for calculating the Z-score. BMI Z-scores for adults was calculated using the oldest available age (20 years) from the CDC growth charts.

End point type	Other pre-specified

End point timeframe:

RW Period Baseline to Week 16.

End point values	DCCR (Double-blind)	Placebo for DCCR (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: BMI-Z Score				
least squares mean (standard error)	-0.02 (± 0.031)	0.07 (± 0.031)		

Statistical analyses

Statistical analysis title	Additional endpoint - BMI Z-score

Statistical analysis description:

Missing values were not imputed, and data collected after treatment discontinuation are included. LS Means are based on an ANCOVA model adjusting for RW Baseline BMI Z-score and RW Baseline HQ-CT Total Score category (<13 versus 13-36).

Comparison groups	DCCR (Double-blind) v Placebo for DCCR (Double-blind)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0233
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.04

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study medication in C602 study period through end of study period + 2 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	DCCR (Open-label)
Reporting group description: Once daily oral administration of open-label study medication.	
Reporting group title	DCCR (Double-blind)
Reporting group description: Once daily oral administration of double-blind study medication.	
Reporting group title	Placebo for DCCR (Double-blind)
Reporting group description: Once daily oral administration of double-blind study medication.	

Serious adverse events	DCCR (Open-label)	DCCR (Double-blind)	Placebo for DCCR (Double-blind)
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 115 (13.91%)	0 / 38 (0.00%)	1 / 39 (2.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Foreign body ingestion			
subjects affected / exposed	2 / 115 (1.74%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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

Tibia fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Volvulus			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Vomiting			
subjects affected / exposed	2 / 115 (1.74%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Psychiatric disorders			
Abnormal behaviour			

subjects affected / exposed	2 / 115 (1.74%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Dermatillomania			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Homicidal ideation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Major depression			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Suicidal behaviour			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Suicidal ideation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Gastroenteritis Escherichia coli			

subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 115 (0.00%)	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 115 (0.87%)	0 / 38 (0.00%)	0 / 39 (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

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

Non-serious adverse events	DCCR (Open-label)	DCCR (Double-blind)	Placebo for DCCR (Double-blind)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	114 / 115 (99.13%)	28 / 38 (73.68%)	29 / 39 (74.36%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 115 (7.83%)	2 / 38 (5.26%)	2 / 39 (5.13%)
occurrences (all)	9	2	2
Oedema peripheral			
subjects affected / exposed	39 / 115 (33.91%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	71	0	0
Pyrexia			

subjects affected / exposed	13 / 115 (11.30%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	19	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	12 / 115 (10.43%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	18	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 115 (13.91%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	17	0	0
Nasal congestion			
subjects affected / exposed	8 / 115 (6.96%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	14	0	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	11 / 115 (9.57%)	5 / 38 (13.16%)	5 / 39 (12.82%)
occurrences (all)	12	5	5
Affect lability			
subjects affected / exposed	0 / 115 (0.00%)	3 / 38 (7.89%)	1 / 39 (2.56%)
occurrences (all)	0	3	1
Aggression			
subjects affected / exposed	9 / 115 (7.83%)	3 / 38 (7.89%)	5 / 39 (12.82%)
occurrences (all)	18	3	7
Anger			
subjects affected / exposed	0 / 115 (0.00%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Anxiety			
subjects affected / exposed	13 / 115 (11.30%)	4 / 38 (10.53%)	2 / 39 (5.13%)
occurrences (all)	13	4	3
Behaviour disorder			
subjects affected / exposed	7 / 115 (6.09%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	8	0	0
Compulsive hoarding			
subjects affected / exposed	0 / 115 (0.00%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Dermatillomania			

subjects affected / exposed	21 / 115 (18.26%)	5 / 38 (13.16%)	6 / 39 (15.38%)
occurrences (all)	29	8	8
Sleep disorder			
subjects affected / exposed	0 / 115 (0.00%)	1 / 38 (2.63%)	3 / 39 (7.69%)
occurrences (all)	0	1	4
Suicidal ideation			
subjects affected / exposed	0 / 115 (0.00%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	0	2	1
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	6 / 115 (5.22%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	7	0	0
Weight increased			
subjects affected / exposed	7 / 115 (6.09%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	9	2	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	6 / 115 (5.22%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	7	0	0
Contusion			
subjects affected / exposed	7 / 115 (6.09%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	7	0	0
Ligament sprain			
subjects affected / exposed	8 / 115 (6.96%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	12	0	0
Procedural pain			
subjects affected / exposed	8 / 115 (6.96%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	9	0	0
Skin abrasion			
subjects affected / exposed	6 / 115 (5.22%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	7	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 115 (24.35%)	0 / 38 (0.00%)	3 / 39 (7.69%)
occurrences (all)	67	0	4
Repetitive speech			

subjects affected / exposed	0 / 115 (0.00%)	2 / 38 (5.26%)	2 / 39 (5.13%)
occurrences (all)	0	2	2
Somnolence			
subjects affected / exposed	12 / 115 (10.43%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	13	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	8 / 115 (6.96%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	13	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 115 (10.43%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	15	0	0
Abdominal pain upper			
subjects affected / exposed	8 / 115 (6.96%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	12	0	0
Constipation			
subjects affected / exposed	13 / 115 (11.30%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	21	0	0
Diarrhoea			
subjects affected / exposed	11 / 115 (9.57%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	14	0	0
Tooth impacted			
subjects affected / exposed	8 / 115 (6.96%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	8	0	0
Vomiting			
subjects affected / exposed	6 / 115 (5.22%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	9	0	0
Skin and subcutaneous tissue disorders			
Hirsutism			
subjects affected / exposed	31 / 115 (26.96%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	48	2	1
Hypertrichosis			
subjects affected / exposed	72 / 115 (62.61%)	2 / 38 (5.26%)	5 / 39 (12.82%)
occurrences (all)	117	2	5
Pruritus			

subjects affected / exposed	7 / 115 (6.09%)	0 / 38 (0.00%)	2 / 39 (5.13%)
occurrences (all)	7	0	2
Rash			
subjects affected / exposed	10 / 115 (8.70%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	11	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 115 (11.30%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	16	0	0
Back pain			
subjects affected / exposed	7 / 115 (6.09%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	9	0	0
Pain in extremity			
subjects affected / exposed	17 / 115 (14.78%)	0 / 38 (0.00%)	3 / 39 (7.69%)
occurrences (all)	31	0	4
Infections and infestations			
COVID-19			
subjects affected / exposed	25 / 115 (21.74%)	0 / 38 (0.00%)	2 / 39 (5.13%)
occurrences (all)	26	0	2
Ear infection			
subjects affected / exposed	14 / 115 (12.17%)	2 / 38 (5.26%)	3 / 39 (7.69%)
occurrences (all)	20	2	4
Gastrointestinal viral infection			
subjects affected / exposed	6 / 115 (5.22%)	0 / 38 (0.00%)	2 / 39 (5.13%)
occurrences (all)	7	0	2
Influenza			
subjects affected / exposed	12 / 115 (10.43%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	12	0	0
Nasopharyngitis			
subjects affected / exposed	18 / 115 (15.65%)	1 / 38 (2.63%)	4 / 39 (10.26%)
occurrences (all)	28	1	4
Pharyngitis streptococcal			
subjects affected / exposed	0 / 115 (0.00%)	2 / 38 (5.26%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Sinusitis			

subjects affected / exposed	10 / 115 (8.70%)	1 / 38 (2.63%)	2 / 39 (5.13%)
occurrences (all)	13	1	2
Upper respiratory tract infection			
subjects affected / exposed	22 / 115 (19.13%)	2 / 38 (5.26%)	1 / 39 (2.56%)
occurrences (all)	32	3	1
Urinary tract infection			
subjects affected / exposed	10 / 115 (8.70%)	1 / 38 (2.63%)	2 / 39 (5.13%)
occurrences (all)	14	1	2
Viral infection			
subjects affected / exposed	6 / 115 (5.22%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	7	0	0
Metabolism and nutrition disorders			
Food craving			
subjects affected / exposed	6 / 115 (5.22%)	3 / 38 (7.89%)	4 / 39 (10.26%)
occurrences (all)	6	4	4
Hyperglycaemia			
subjects affected / exposed	27 / 115 (23.48%)	0 / 38 (0.00%)	0 / 39 (0.00%)
occurrences (all)	36	0	0
Hyperphagia			
subjects affected / exposed	7 / 115 (6.09%)	4 / 38 (10.53%)	1 / 39 (2.56%)
occurrences (all)	7	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2019	(Amendment 1) Extended study duration from 40 weeks to 54 weeks. Added fasting glucose measurement by glucometer on telephone call visit days and recording of levels in a paper diary. Added identification of used study medication cards as a source document since this is the first point of entry of the date and time the study medication was taken. Added Weight Band 0, for participants weighing 20 to <30 kg. Dose adjustments: 1) clarified that dose may be adjusted if the participant either loses or gains a significant amount of weight; 2) moved the option to adjust dose to Visit 6 (Week 13) and Visit 7 (Week 17).
18 June 2019	(Amendment 1a) Modified exclusion criterion 5 related to a new history in participant's first degree relative or change in participant's physical examination that may significantly increase the participant's risk for thromboembolic event. Added an ECG to be performed 18–24 hours after first dose of study medication (i.e., Visit 1) but prior to the second dose, for participants taking concomitant citalopram or escitalopram. This additional ECG is required only for participants who are currently taking citalopram or escitalopram. Removed reference to non-fasting blood tests as all blood tests will now be completed fasting. Clarified that fasting blood tests will be completed at Visit 1–6, inclusive.
26 September 2019	(Amendment 2) Added details pertaining to the C602 Extension. Updated the reason for possible study discontinuation. Clarified dose adjustment criteria for subjects participating in the C602 Extension. Updated assessments for subjects taking specific concomitant medications.
01 October 2020	(Amendment 3) Updated study duration to 5 years and changed the requirement for certain visits to be conducted via telephone versus In-Clinic. Removed the optional Home Health Nurse Visits. Revised Schedule of Events accordingly. Re-organised the Efficacy Endpoints and Exploratory Endpoints and added additional Endpoints. Clarified study early discontinuation and subject withdrawal criteria. Updated study assessments. Updated definition of baseline for the purposes of analyses.
07 October 2020	(Amendment 4) Added "Efficacy" to the title and applicable sections because the efficacy data in this study may be used to support the benefits of DCCR. Generalized description of packaging of study drug as packaging transitioned from study medication cards to bottles during this study; added details to Dose Description to support this change. Updated secondary and additional study objectives. Modified safety, efficacy, and exploratory endpoints and specified timepoints for endpoint evaluation to support changes in trial objectives. Modified requirements for subject withdrawal. Specified conditions for End of Study Visit. Updated criteria for dose adjustments and added a section on dose adjustments due to adverse events. Added section on contingency measures to the conduct of the study as a result of the COVID-19 Pandemic. Updated the statistical analysis section.

18 May 2022	(Amendment 5) Added randomized withdrawal period (RW Period) to obtain additional controlled data by comparing participants who are randomized to continue DCCR treatment versus those randomized to placebo. As a result, the protocol title was revised, and text was provided, or new sections were added for the following: Dose Selection Rationale, Study Duration Rationale, Population, Trial Objectives, Study Endpoints, Study Design, Randomization, Blinding, Additional Steps taken to Minimize/Avoid Bias, Packaging and Labeling, Duration of Study Participation, Discontinuation of Study, RW Period Eligibility Assessments, Participant Withdrawal, Treatments to be Administered, Dose Maintenance, Dose Adjustments, Medications, Informed Consent/Assent, Randomization into RW Period, Monitoring of Lab Results, Clinical Global Impression of Improvement (CGI-I), Hyperphagia Questionnaire for Clinical Trials (HQ-CT), PWS Profile (PWSP) Questionnaire, Individual Participant Experience Through Semi-Structured Caregiver Interviews, RW Period End of Study, and Schedule of Events. Furthermore, the Statistical Plan sections for Introduction, Sample Size Considerations, Analysis Populations, Safety Analyses, Efficacy Analyses, Subgroup Analyses, Pharmacokinetic Analysis, Termination Criteria, Interim Analyses and Handling of Missing Data were added or updated to describe aspects of the OLE Period and RW Period.
26 August 2022	(Amendment 6) Updated primary and secondary objectives, efficacy endpoints, efficacy analysis descriptions, randomisation stratification, exclusion criteria, sample size and the control of type 1 error and risk/benefit section. Clarifications were made to clearly indicate that the Sponsor is discontinuing the Open-Label Extension (OLE) Period. Updated to study assessments, visit schedule, Schedule of Events, and duration of participants in the RW Period. Added to guidance on the caregiver's responsibilities prior to study visits. Updated the description of the Randomised Withdrawal Intent-to-Treat (RWITT) Population and subgroup analyses.
11 November 2022	(Amendment 7) Added CGI-S to the secondary objectives and 5 domain-specific CGI-S scales to the exploratory objectives. Clarified the definition of the Randomised Withdrawal Intent-to-Treat (RWITT) Population.

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/37919617