Clinical trial results:
Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant

Summary

EudraCT number	2018-003096-35
Trial protocol	NL BG AT PL ES DE IT RO
Global end of trial date	15 April 2024

Results information

Result version number	v1 (current)
This version publication date	10 July 2025
First version publication date	10 July 2025

Trial information

Trial identification

Sponsor protocol code	CORT125134-455

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03697109
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Corcept Therapeutics Incorporated
Sponsor organisation address	101 Redwood Shores Parkway, Redwood City, United States, 94065
Public contact	Medical Director, Corcept Therapeutics Incorporated, +1 650-327-3270, corceptstudy455@corcept.com
Scientific contact	Medical Director, Corcept Therapeutics Incorporated, +1 650-327-3270, corceptstudy455@corcept.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 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 3, double-blind, placebo-controlled, randomized-withdrawal study to assess the efficacy, safety and pharmacokinetics (PK) of relacorilant in patients with endogenous Cushing syndrome and concurrent type 2 diabetes mellitus/impaired glucose tolerance (DM/IGT) and/or uncontrolled hypertension (HTN).

The first primary endpoint is the assessment of efficacy of relacorilant treatment based on sustained blood pressure control during the Randomized-withdrawal (RW) Phase, wherein patients who had achieved the blood pressure response criteria during the Open-label (OL) Phase are randomized to receive either relacorilant or placebo for 12 weeks. The second primary endpoint is assessment of safety as the number of patients with 1 or more treatment-emergent adverse events (TEAEs).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2018
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	Netherlands: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 70
Worldwide total number of subjects	152
EEA total number of subjects	76

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	127
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 404 patients were screened and 152 were enrolled.

Period 1

Period 1 title	Open-label (OL) Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Relacorilant (OL Phase)

Arm description:

Patients will receive relacorilant increased sequentially from 100 mg once daily to a maximum dose of 400 mg once daily.

Arm type	Experimental
Investigational medicinal product name	Relacorilant
Investigational medicinal product code	
Other name	CORT125134
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Relacorilant is supplied as 100 mg capsules for oral dosing.

Number of subjects in period 1	Relacorilant (OL Phase)
Started	152
Completed	95
Not completed	57
Adverse event, serious fatal	2
Consent withdrawn by subject	21
Physician decision	2
Adverse event, non-fatal	24
Lost to follow-up	2
Lack of efficacy	6

Period 2

Period 2 title	Randomized-withdrawal (RW) Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Relacorilant (RW Phase)

Arm description:

Patients who meet any of the response criteria will advance to the RW Phase of the study and receive the same dose of relacorilant as the last dose administered in the OL Phase.

Arm type	Experimental
Investigational medicinal product name	Relacorilant
Investigational medicinal product code	
Other name	CORT125134
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Relacorilant is supplied as 100 mg capsules for oral dosing.

Arm title	Placebo (RW Phase)

Arm description:

Patients who meet any of the response criteria will advance to the RW Phase of the study and receive placebo matched to study drug.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to study drug.

Number of subjects in period 2[1]	Relacorilant (RW Phase)	Placebo (RW Phase)
Started	30	32
Completed	27	31
Not completed	3	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
Lack of efficacy	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 95 patients who completed the OL Phase, 33 did not qualify or chose not to enter the RW Phase. Thus, a total of 62 patients entered the RW Phase of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Relacorilant (OL Phase)
Reporting group description:	
Patients will receive relacorilant increased sequentially from 100 mg once daily to a maximum dose of 400 mg once daily.	

Reporting group values	Relacorilant (OL Phase)	Total	
Number of subjects	152	152	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	127	127	
From 65-84 years	25	25	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	50.4		
standard deviation	± 13.23	-	
Gender categorical			
Units: Subjects			
Female	127	127	
Male	25	25	
Hypertension (HTN), Diabetes mellitus (DM), and impaired glucose tolerance (IGT) Status			
HTN is defined as mean systolic blood pressure (SBP) ≥135 or ≤170 mm Hg and/or mean diastolic blood pressure (DBP) ≥85 to ≤110 mm Hg. DM is defined as fasting plasma glucose ≥126 mg/dL and/or oral glucose tolerance test plasma glucose ≥200 mg/dL or hemoglobin A1c (HbA1c) ≥6.5%. IGT is defined as plasma glucose ≥140 mg/dL and <200 mg/dL on a 2-hour oral glucose tolerance test.			
Units: Subjects			
HTN only	31	31	
DM or IGT only	50	50	
HTN and DM/IGT	71	71	
Body Weight			
Units: Kg			
arithmetic mean	93.77		
standard deviation	± 24.660	-	
Body Mass Index (BMI)			
Units: Kg/m^2			
arithmetic mean	34.738		
standard deviation	± 32.675	-	
Waist circumference			

Units: cm			
arithmetic mean	114.85		
standard deviation	± 18.0355	-	

End points

End points reporting groups

Reporting group title	Relacorilant (OL Phase)
Reporting group description:	
Patients will receive relacorilant increased sequentially from 100 mg once daily to a maximum dose of 400 mg once daily.	
Reporting group title	Relacorilant (RW Phase)
Reporting group description:	
Patients who meet any of the response criteria will advance to the RW Phase of the study and receive the same dose of relacorilant as the last dose administered in the OL Phase.	
Reporting group title	Placebo (RW Phase)
Reporting group description:	
Patients who meet any of the response criteria will advance to the RW Phase of the study and receive placebo matched to study drug.	

Primary: Number of Patients With Loss of Response With Respect to Hypertension During the RW Phase.

End point title	Number of Patients With Loss of Response With Respect to Hypertension During the RW Phase.
End point description:	
Loss of response with respect to HTN was measured using 6 criteria: 1) an increase in SBP of at least 5 mm Hg, 2) an increase in DBP of at least 5 mm Hg, 3) an increase in SBP and/or DBP of at least 5 mm Hg, 4) use of HTN rescue medication, 5) treatment discontinuation, and 6) missing 24-hour ambulatory blood pressure monitoring (ABPM) measurement at the end of the RW Phase. Blood pressure was measured using ABPM. Use of rescue medication was defined as any increase, modification, or addition of antihypertensive medication due to worsening HTN. Treatment discontinuation reports the number of patients who discontinued study treatment in the RW Phase for any reason. The analysis population was patients in the Intent-to-Treat (ITT-RW) Population who met the HTN response criteria at conclusion of the OL Phase. The ITT-RW Population included all patients who were randomized in the RW Phase and received at least 1 dose of study drug post randomization.	
End point type	Primary
End point timeframe:	
Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)	

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	22		
Units: Patients				
SBP	3	1		
DBP	1	1		
SBP and/or DBP	3	4		
Use of rescue medication	0	7		
Treatment discontinuation	2	3		
Missing ABPM at end of RW Phase	2	3		

Statistical analyses

Statistical analysis title	Difference in Loss of HTN Response

Statistical analysis description:

The analysis is the difference in total count of patients losing HTN response between (continuing) relacorilant and placebo (withdrawing relacorilant) treatment in patients with initial HTN response to relacorilant.

Comparison groups	Relacorilant (RW Phase) v Placebo (RW Phase)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.0215
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.77

Notes:

[1] - A logistic regression model with logit link function was used in order to detect if there was a significant difference in the proportion of patients with a loss of response with respect to hypertension under treatment with relacorilant compared with treatment with placebo in the RW Phase.

Primary: Number of Patients With 1 or More Treatment-emergent Adverse Events (TEAEs) as Graded by CTCAE v5.0.

End point title	Number of Patients With 1 or More Treatment-emergent Adverse Events (TEAEs) as Graded by CTCAE v5.0.[2]

End point description:

The analysis population was patients in the Safety Population, which included all enrolled patients who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

OL Phase: Up to 22 weeks; RW Phase: up to 18 weeks after completion of the OL Phase

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: No between-group statistical analysis was planned or conducted for this endpoint.

End point values	Relacorilant (OL Phase)	Relacorilant (RW Phase)	Placebo (RW Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	30	32	
Units: Patients	147	23	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Area Under the Concentration-time Curve of Blood Glucose (AUCglucose) During the RW Phase

End point title	Change in Area Under the Concentration-time Curve of Blood

	Glucose (AUCglucose) During the RW Phase

End point description:

The analysis population was patients in the ITT-RW Population who had DM/IGT with or without HTN at Baseline.

End point type	Secondary

End point timeframe:

Before and at time intervals up to 2 hours post glucose drink at Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: hours x mmol/L				
least squares mean (confidence interval 95%)	1.91 (-1.138 to 4.966)	4.81 (2.096 to 7.529)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hemoglobin HbA1c During the RW Phase

End point title	Change in Hemoglobin HbA1c During the RW Phase

End point description:

The analysis population was patients in the ITT-RW Population who had DM/IGT with or without HTN at Baseline.

End point type	Secondary

End point timeframe:

Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	19		
Units: Percentage of HbA1c				
least squares mean (confidence interval 95%)	0.06 (-0.270 to 0.383)	0.28 (-0.022 to 0.578)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 2-hour Plasma Glucose During the RW Phase

End point title	Change in 2-hour Plasma Glucose During the RW Phase

End point description:

Plasma glucose was measured using the 2-hour Oral Glucose Tolerance Test (oGTT). The analysis population was patients in the ITT-RW Population who had DM/IGT with or without HTN at Baseline.

End point type	Secondary

End point timeframe:

Before and 2 hours post glucose drink at Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: mmol/L				
least squares mean (confidence interval 95%)	0.52 (-1.06 to 2.09)	2.96 (1.55 to 4.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SBP and DBP During the RW Phase

End point title	Change in SBP and DBP During the RW Phase

End point description:

Blood pressure was measured by 24-hour ABPM. The analysis population was patients in the ITT-RW Population who had HTN with or without DM/IGT at Baseline.

End point type	Secondary

End point timeframe:

Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	22		
Units: mm Hg				
least squares mean (confidence interval 95%)				
SBP	3.95 (0.470 to 7.424)	10.43 (6.538 to 14.329)		
DBP	2.86 (-0.199 to 5.928)	6.53 (3.224 to 9.832)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Body Weight During the RW Phase

End point title	Change in Body Weight During the RW Phase

End point description:

The analysis population was patients in the ITT-RW Population.

End point type	Secondary

End point timeframe:

Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: kg				
least squares mean (confidence interval 95%)	-1.21 (-2.685 to 0.269)	0.54 (-0.851 to 1.939)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Any Increase or Modification in Diabetes Medication During the RW Phase

End point title	Number of Patients With Any Increase or Modification in Diabetes Medication During the RW Phase

End point description:

The analysis population was patients in the ITT-RW Population who had DM/IGT at Baseline and received antidiabetic medication during the RW Phase.

End point type	Secondary

End point timeframe:

Week 22 (end of OL Phase) and up to Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Patients	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cushing Quality of Life (QoL) Normalized Total Score During the RW Phase

End point title	Change in Cushing Quality of Life (QoL) Normalized Total Score During the RW Phase

End point description:

The Cushing QoL patient questionnaire, which evaluates the health-related QoL in patients with Cushing syndrome, comprises 12 questions, each with 5 possible answers. The total score ranges from 12-60, with a higher score indicating improvement in QoL. The Cushing QoL instrument addresses known problem areas associated with Cushing syndrome including trouble sleeping, wound healing/bruising, irritability/mood swings/anger, self-confidence, physical changes, ability to participate in activities, interactions with friends and family, memory issues, and future health concerns. The analysis population was patients in the ITT-RW Population.

End point type	Secondary

End point timeframe:

Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: Score on a scale				
least squares mean (confidence interval 95%)	0.59 (-4.28 to 5.46)	-0.58 (-5.14 to 3.98)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Tissue Fat Mass During the RW Phase

End point title	Percent Change in Tissue Fat Mass During the RW Phase

End point description:

Tissue fat mass was measured by dual energy X-ray absorptiometry (DXA) scan. Reported are change in in absolute tissue fat mass and change in percent tissue fat mass. The analysis population was patients in the ITT-RW Population.

End point type	Other pre-specified

End point timeframe:

Week 22 (end of OL Phase) and Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: Percent change				
least squares mean (confidence interval 95%)				
Absolute Tissue Fat Mass	-0.64 (-1.684 to 0.400)	1.67 (0.776 to 2.573)		

Percent Tissue Fat Mass	-0.14 (-1.031 to 0.759)	1.66 (0.887 to 2.437)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients Who Worsened, as Assessed by the Global Clinical Response, During the RW Phase

End point title	Number of Patients Who Worsened, as Assessed by the Global Clinical Response, During the RW Phase

End point description:

The Global Clinical Response assessment measures the patient's signs and symptoms of endogenous hypercortisolism in 7 clinical categories: 1) glucose parameters, 2) blood pressure parameters, 3) body composition parameters, 4) clinical appearance, 5) strength parameters, 6) psychiatric health/cognitive function parameters, and 7) quality of life using the Cushing QoL score. The overall response based on the totality of signs and symptoms is rated as +1 for improved, 0 for unchanged, and -1 for worsened. Each patient's final score is the median of ratings given by 3 members of the Data Review Board.

End point type	Other pre-specified

End point timeframe:

Week 22 (end of OL Phase) and up to Week 36 (Week 12 of RW Phase)

End point values	Relacorilant (RW Phase)	Placebo (RW Phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Patients				

Notes:

[3] - End point data not reported

[4] - End point data not reported

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Percent Tissue Fat Mass During the OL Phase

End point title	Change in Percent Tissue Fat Mass During the OL Phase

End point description:

Tissue fat mass was measured by DXA scan. The analysis population was patients in the modified ITT-OL (mITT-OL) Population including all enrolled patients who received at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	151[5]			
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline Percent Tissue Fat Mass OL Phase	46.4 (± 8.39)			
Change in Percent Tissue Fat Mass Week 22	-1.8 (± 2.73)			

Notes:

[5] - n=131 for Baseline value; n=71 for Change value

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Cushing QoL Normalized Total Score During the OL Phase

End point title	Change in Cushing QoL Normalized Total Score During the OL Phase

End point description:

The Cushing QoL patient questionnaire, which evaluates the health-related QoL in patients with Cushing syndrome, comprises 12 questions, each with 5 possible answers. The total score ranges from 12-60, with a higher score indicating improvement in QoL. The Cushing QoL instrument addresses known problem areas associated with Cushing syndrome including trouble sleeping, wound healing/bruising, irritability/mood swings/anger, self-confidence, physical changes, ability to participate in activities, interactions with friends and family, memory issues, and future health concerns. The analysis population was patients in the mITT-OL Population.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	151[6]			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline Cushing QoL Score	41.9 (± 19.78)			
Change from Baseline in Cushing QoL Score	7.4 (± 14.63)			

Notes:

[6] - n=151 for Baseline value; n=99 for Change value

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Beck Depression Inventory-II (BDI-II) Score During the OL Phase

End point title	Change in Beck Depression Inventory-II (BDI-II) Score During

	the OL Phase

End point description:

The BDI-II is a 21-question self-report inventory that measures depression. Each answer is scored with values of 0 to 3. The total score ranges from 0 to 63. Scores of 0 to 13 indicate minimal depression, 14 to 19; mild depression; 20 to 28; moderate depression; 29 to 63; severe depression. The analysis population was patients in the mITT-OL Population.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	151[7]			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline BDI-II Score	16.0 (± 10.24)			
Change from Baseline in BDI-II Score at Week 22	-2.8 (± 8.91)			

Notes:

[7] - n=151 for Baseline value; n=99 for Change value

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline in Body Weight During the OL Phase

End point title	Mean Change From Baseline in Body Weight During the OL Phase

End point description:

The analysis population was patients in the mITT-OL Population.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	151[8]			
Units: kg				
arithmetic mean (standard deviation)				
Baseline Body Weight	93.82 (± 24.734)			
Change from Baseline in Body Weight at Week 22	-3.31 (± 5.861)			

Notes:

[8] - n=151 for Baseline value; n=97 for Change value

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in 2-hour Plasma Glucose During the OL Phase

End point title	Change in 2-hour Plasma Glucose During the OL Phase

End point description:

Plasma glucose was measured using the 2-hour oGTT. The analysis population was patients in the mITT-OL Population who had DM/IGT with or without HTN at Baseline.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	120[9]			
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline oGTT	14.370 (± 4.9402)			
Change from Baseline in oGTT at Week 22	-2.117 (± 4.6354)			

Notes:

[9] - n=119 for Baseline value; n=71 for Change value

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Hemoglobin HbA1c During the OL Phase

End point title	Change in Hemoglobin HbA1c During the OL Phase

End point description:

The analysis population was patients in the mITT-OL Population who had DM/IGT at Baseline.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	120[10]			
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Baseline HbA1c	7.16 (± 1.626)			
Change from Baseline in HbA1c at Week 22	-0.29 (± 1.014)			

Notes:

[10] - n=120 for Baseline value; n=74 for Change value

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in SBP and DBP During the OL Phase

End point title	Change in SBP and DBP During the OL Phase

End point description:

Blood pressure was measured by 24-hour ABPM. The analysis population was patients in the mITT-OL Population who had HTN at Baseline.

End point type	Other pre-specified

End point timeframe:

Baseline and Week 22 (end of OL Phase)

End point values	Relacorilant (OL Phase)			
Subject group type	Reporting group			
Number of subjects analysed	102[11]			
Units: mm Hg				
arithmetic mean (standard deviation)				
Baseline SBP	140.6 (± 10.66)			
Change from Baseline in SBP at Week 22	-7.9 (± 9.78)			
Baseline DBP	88.9 (± 7.20)			
Change from Baseline in DBP at Week 22	-5.4 (± 6.98)			

Notes:

[11] - n=101 for the Baseline values; n=66 for the Change values

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: OL Phase: Up to 22 weeks; RW Phase: up to 18 weeks after completion of the OL Phase.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Relacorilant (OL Phase)
Reporting group description: Patients will receive relacorilant increased sequentially from 100 mg once daily to a maximum dose of 400 mg once daily.	
Reporting group title	Relacorilant (RW Phase)
Reporting group description: Patients who meet any of the response criteria will advance to the RW Phase of the study and receive the same dose of relacorilant as the last dose administered in the OL Phase.	
Reporting group title	Placebo (RW Phase)
Reporting group description: Patients who meet any of the response criteria will advance to the RW Phase of the study and receive placebo matched to study drug.	

Serious adverse events	Relacorilant (OL Phase)	Relacorilant (RW Phase)	Placebo (RW Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 152 (19.08%)	5 / 30 (16.67%)	1 / 32 (3.13%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Squamous cell carcinoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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 disorders			
Hypotension			

subjects affected / exposed	3 / 152 (1.97%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granuloma			
subjects affected / exposed	0 / 152 (0.00%)	1 / 30 (3.33%)	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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 152 (1.32%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Pelvic fracture			

subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Congenital, familial and genetic disorders			
Congenital mitral valve incompetence			
subjects affected / exposed	0 / 152 (0.00%)	0 / 30 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 152 (1.32%)	0 / 30 (0.00%)	0 / 32 (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
Cardiac failure chronic			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Myocardial infarction			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Eye disorders			
Eye oedema			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Hiatus hernia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Pancreatitis acute			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 152 (1.32%)	0 / 30 (0.00%)	0 / 32 (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
Chronic kidney disease			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Nephrolithiasis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Osteoporosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Rhabdomyolysis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bone abscess			

subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cavernous sinus thrombosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 152 (0.66%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Pseudomonal sepsis			
subjects affected / exposed	1 / 152 (0.66%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Sepsis			

subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Sinusitis fungal			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal osteomyelitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Urinary tract infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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
Wound abscess			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (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 / 1	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 30 (3.33%)	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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 152 (1.32%)	0 / 30 (0.00%)	0 / 32 (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
Hypoglycaemia			

subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 152 (0.66%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	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	Relacorilant (OL Phase)	Relacorilant (RW Phase)	Placebo (RW Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 152 (96.71%)	22 / 30 (73.33%)	27 / 32 (84.38%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 152 (0.00%)	0 / 30 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 152 (6.58%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	14	0	0
Hypertension			
subjects affected / exposed	0 / 152 (0.00%)	1 / 30 (3.33%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 152 (20.39%)	3 / 30 (10.00%)	4 / 32 (12.50%)
occurrences (all)	57	3	8
Dizziness			
subjects affected / exposed	23 / 152 (15.13%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	28	0	0

Paraesthesia			
subjects affected / exposed	21 / 152 (13.82%)	2 / 30 (6.67%)	0 / 32 (0.00%)
occurrences (all)	30	5	0
Neuropathy peripheral			
subjects affected / exposed	13 / 152 (8.55%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	14	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 30 (3.33%)	2 / 32 (6.25%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	50 / 152 (32.89%)	2 / 30 (6.67%)	1 / 32 (3.13%)
occurrences (all)	60	3	1
Fatigue			
subjects affected / exposed	34 / 152 (22.37%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	41	0	0
Asthenia			
subjects affected / exposed	19 / 152 (12.50%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	19	0	0
Peripheral swelling			
subjects affected / exposed	15 / 152 (9.87%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	19	0	0
Pain			
subjects affected / exposed	13 / 152 (8.55%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	13	0	0
Pyrexia			
subjects affected / exposed	0 / 152 (0.00%)	2 / 30 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Increased tendency to bruise			
subjects affected / exposed	0 / 152 (0.00%)	2 / 30 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	52 / 152 (34.21%)	2 / 30 (6.67%)	1 / 32 (3.13%)
occurrences (all)	78	2	1

Diarrhoea			
subjects affected / exposed	28 / 152 (18.42%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	32	0	0
Abdominal pain upper			
subjects affected / exposed	23 / 152 (15.13%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	31	0	0
Constipation			
subjects affected / exposed	23 / 152 (15.13%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	24	0	0
Vomiting			
subjects affected / exposed	19 / 152 (12.50%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	24	0	0
Abdominal pain			
subjects affected / exposed	17 / 152 (11.18%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	19	0	0
Dyspepsia			
subjects affected / exposed	8 / 152 (5.26%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	8	0	0
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	24 / 152 (15.79%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	31	0	0
Acne			
subjects affected / exposed	12 / 152 (7.89%)	3 / 30 (10.00%)	0 / 32 (0.00%)
occurrences (all)	12	3	0
Dry skin			
subjects affected / exposed	9 / 152 (5.92%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	9	0	0
Rash			
subjects affected / exposed	9 / 152 (5.92%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	13	0	0
Pruritus			
subjects affected / exposed	8 / 152 (5.26%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	9	0	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	12 / 152 (7.89%)	0 / 30 (0.00%)	4 / 32 (12.50%)
occurrences (all)	14	0	4
Irritability			
subjects affected / exposed	0 / 152 (0.00%)	2 / 30 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	0 / 152 (0.00%)	1 / 30 (3.33%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	43 / 152 (28.29%)	2 / 30 (6.67%)	2 / 32 (6.25%)
occurrences (all)	83	2	2
Back pain			
subjects affected / exposed	41 / 152 (26.97%)	5 / 30 (16.67%)	6 / 32 (18.75%)
occurrences (all)	59	6	8
Arthralgia			
subjects affected / exposed	30 / 152 (19.74%)	3 / 30 (10.00%)	3 / 32 (9.38%)
occurrences (all)	56	4	6
Myalgia			
subjects affected / exposed	21 / 152 (13.82%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	29	0	0
Muscular weakness			
subjects affected / exposed	17 / 152 (11.18%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	20	0	0
Muscle spasms			
subjects affected / exposed	9 / 152 (5.92%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	11	0	0
Bursitis			
subjects affected / exposed	0 / 152 (0.00%)	3 / 30 (10.00%)	0 / 32 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 152 (7.24%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	11	0	0
Covid-19			

subjects affected / exposed	9 / 152 (5.92%)	2 / 30 (6.67%)	0 / 32 (0.00%)
occurrences (all)	9	2	0
Folliculitis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 30 (3.33%)	2 / 32 (6.25%)
occurrences (all)	0	1	4
Nasopharyngitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 30 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 152 (11.18%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	17	0	0
Hypokalaemia			
subjects affected / exposed	8 / 152 (5.26%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	9	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2019	Clarified the definition of study endpoints and statistical methods on estimation of safety, tolerability, and preliminary efficacy.
29 October 2019	1. Outlined methods to determine when rescue therapy (not resulting in unblinding of study treatment) should be initiated. 2. Added use of an unblinded Medical Monitor. 3. Specified which study-assessment results should remain blinded.
20 December 2019	1. Implementation of changes noted in Clarification Memo dated 06 December 2019 which includes: Clarification that only surgeries associated with radiation therapy are excluded during the study, and clarification of the allowable window for the administration of study drug in relation to the completion of the 2-hour oGTT test. 2. Revised text for rescue criterion in the RW Phase.
17 December 2020	1. Added section to address potential protocol modifications arising from the COVID-19 pandemic that accounts for all deviations and ensures appropriate safety monitoring is followed for trial participants. 2. Modified exclusion criteria based on regulatory agency input. 3. Clarified that dose increases of relacorilant will occur as tolerated and based on improvement in signs and symptoms of Cushing syndrome. 4. Added factors used for the determination of clinical benefit required for patients to continue relacorilant treatment in an extension study. 5. Clarified that if all symptoms of Cushing syndrome have resolved, no dose escalation will occur. 6. Clarified the conditions under which faster dose escalation for patients whose Cushing syndrome deteriorates may be allowed. 7. Added rescue criterion for initiating or increasing rescue medication for patients in the DM/IGT only subgroup. 8. Added details on assessments to be performed in the event rescue medication is used before Visit RW12. 9. Revised criteria for when patients should discontinue study drug/study participation and revised and clarified when return visits should occur following ET. 10. Added secondary efficacy endpoints and revised others for clarity. 11. Added exploratory efficacy endpoints. 12. Altered assessments at certain visits, so that 2-hour oGTT and HbA1c will be performed for all patients (not only DM/IGT patients) and ABPM (24-hour) will be performed for all patients (not only hypertension patients). 13. Decreased the maximum time between Visit OL22 and randomization to the RW Phase from 4 weeks to 2 weeks. 14. Changed procedure for ABPM (24-hour) prior to the RW12 study visit so it’s completed by the patient at home within 7 days of RW12 visit, rather than initiated in the clinic.
05 April 2023	1. Primary and secondary objectives were revised. 2. Primary, secondary, and exploratory endpoints were revised. 3. The number of patients planned to be enrolled in the study and statistical analyses were revised. 4. Conditions for entry to the RW Phase were revised. 5. The factors for assessing clinical benefit were revised. 6. An inclusion criterion was revised, and an exclusion criterion was revised, and one was added. 7. The dose-escalation process was revised. 8. Conditions regarding screening assessments were revised. 9. The conditions regarding Cushing syndrome medication washout were revised. 10. UFC sample collection requirements were revised. 11. Conditions regarding the salivary cortisol test were revised. 12. Procedure for monitoring AEs was revised and text regarding AE expectedness criteria was revised/deleted. Documentation and follow-up of AEs was also revised. Procedure for informing about pregnancy was revised. 13. Text was added regarding prioritizing safety assessments in the event of COVID-19 restrictions. 14. A section regarding data protection was added. 15. Administrative considerations were revised to be consistent among study protocols.

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.

Two protocol amendments occurred after patient enrollment was completed and included revisions to study endpoints and their analysis methods. These amendments are not included in the Substantial Protocol Amendments (Globally) list.

Notes: