Clinical trial results:
Glucocorticoid Receptor Antagonism in the Treatment of Hypercortisolism in Patients with Cortisol-Secreting Adrenal Adenomas or Hyperplasia (GRADIENT): A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Relacorilant

Summary

EudraCT number	2019-004956-12
Trial protocol	DE PL BG IT RO
Global end of trial date	19 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	CORT125134-456

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04308590
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, GRADIENTstudy@corcept.com
Scientific contact	Medical Director, Corcept Therapeutics Incorporated, +1 650 327-3270, GRADIENTstudy@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	19 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary end points of the study are 1) to assess the efficacy of relacorilant based on blood pressure control at Week 22 compared with placebo, and 2) to assess the safety of relacorilant based on adverse events. Patients will be randomized in a 1:1 ratio to treatment with relacorilant (active drug) or placebo. Patients will receive relacorilant or placebo for 22 weeks. Patients who complete the study may also be eligible to roll over into an extension study.

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	27 July 2020
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	Romania: 16
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	United States: 53
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Austria: 4
Worldwide total number of subjects	137
EEA total number of subjects	75

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	72
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 307 patients were screened, and 137 were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Relacorilant

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 blister-packed capsules for oral dosing. Relacorilant 400 mg dose consists of 4 relacorilant 100-mg capsules. Relacorilant 100-mg, 200-mg, and 300-mg doses are each given as a combination of 4 capsules containing relacorilant 100-mg and placebo as per the assigned dose.

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

Dosage and administration details:

Placebo is supplied as blister-packed capsules for oral dosing. Each dose consists of 4 capsules containing placebo.

Arm title	Placebo

Arm description:

Patients will receive placebo matched to study drug once daily.

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 is supplied as blister-packed capsules for oral dosing. Each dose consists of 4 capsules containing placebo.

Number of subjects in period 1	Relacorilant	Placebo
Started	68	69
Completed	43	61
Not completed	25	8
Adverse event, serious fatal	1	-
Consent withdrawn by subject	10	4
Physician decision	1	-
Adverse event, non-fatal	12	2
Subject does not want to continue with PI	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Relacorilant
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	Placebo
Reporting group description:	
Patients will receive placebo matched to study drug once daily.	

Reporting group values	Relacorilant	Placebo	Total
Number of subjects	68	69	137
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	36	36	72
From 65-84 years	32	33	65
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	62.5	63.0	
standard deviation	± 9.11	± 9.00	-
Gender categorical			
Units: Subjects			
Female	50	49	99
Male	18	20	38
Hypertension (HTN), Diabetes mellitus (DM), and impaired glucose tolerance (IGT) Status			
HTN without diabetes mellitus (DM) or impaired glucose intolerance (IGT). HTN is defined as average systolic blood pressure (SBP) ≥130 to ≤170 mm Hg based on 24-hour ambulatory blood pressure monitoring (ABPM). DM/IGT without HTN. DM is defined as fasting plasma glucose ≥126 mg/dL and/or 2-hour oral glucose tolerance test (oGTT) plasma glucose ≥200 mg/dL, or hemoglobin A1C (HbA1c) ≥6.5%. IGT is defined as plasma glucose ≥140 mg/dL and <200 mg/dL at 2 hours on the 2-hour oGTT.			
Units: Subjects			
HTN only	20	21	41
DM or IGT only	26	27	53
HTN and DM/IGT	22	21	43

End points

End points reporting groups

Reporting group title	Relacorilant
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	Placebo
Reporting group description:	
Patients will receive placebo matched to study drug once daily.	

Primary: Change in Average 24-hour SBP

End point title	Change in Average 24-hour SBP
End point description:	
Blood pressure was measured by 24-hour ABPM. The 24-hour average SBP is reported. The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline.	
End point type	Primary
End point timeframe:	
Baseline and Week 22	

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: mm Hg				
least squares mean (confidence interval 95%)	-5.56 (-10.459 to -0.659)	-2.89 (-6.794 to 1.006)		

Statistical analyses

Statistical analysis title	Difference in Change in Average 24-hour SBP
Statistical analysis description:	
The primary analysis will determine whether there is a difference between treatment groups in terms of change from Baseline to Week 22 in 24-hour average SBP. This was performed using a linear mixed-model-for-repeated-measures (MMRM) analysis using a placebo wash-out multiple imputation for treatment discontinuation and for patients that use rescue medication.	
Comparison groups	Relacorilant v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.416
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.096
upper limit	3.766

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.[1]

End point description:

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

End point type	Primary

End point timeframe:

Baseline and up to Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical analysis was planned or conducted for this end point.

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	69		
Units: Patients	67	60		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change in Area Under the Concentration-time Curve of Blood Glucose (AUCglucose)

End point description:

AUCglucose was calculated based on results of the plasma 2-hour oGTT. The analysis population was patients in the ITT Population who had DM/IGT with or without HTN at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Before and at time intervals up to 2 hours post glucose drink at Baseline and Week 22.

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	38		
Units: hours x mmol/L				
least squares mean (confidence interval 95%)	-1.566 (-3.472 to 0.340)	1.008 (-0.661 to 2.676)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average Diastolic Blood Pressure (DBP)

End point title	Change in Average Diastolic Blood Pressure (DBP)

End point description:

Blood pressure was measured by 24-hour ABPM. Daytime average DBP was measured from 06:00 to 21:59. Nighttime average DBP was measured from 22:00 to 05:59. The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22.

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	30		
Units: mm Hg				
least squares mean (confidence interval 95%)				
24-hour Average	-3.3 (-6.1 to -0.5)	-1.4 (-3.8 to 0.9)		
Daytime Average	-3.1 (-6.0 to -0.1)	-1.0 (-3.5 to 1.6)		
Nighttime Average	-3.0 (-6.4 to 0.5)	-0.6 (-3.5 to 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average Heart Rate (HR)

End point title	Change in Average Heart Rate (HR)

End point description:

Heart rate was measured by 24-hour ABPM. Daytime average HR was measured from 06:00 to 21:59. Nighttime average HR was measured from 22:00 to 05:59. The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22.

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	30		
Units: Beats per minute				
least squares mean (confidence interval 95%)				
24-hour Average	2.0 (-0.4 to 4.5)	-2.0 (-4.1 to 0.1)		
Daytime Average	1.7 (-1.1 to 4.5)	-1.5 (-3.9 to 0.9)		
Nighttime Average	2.2 (-0.4 to 4.7)	-2.7 (-4.9 to -0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average Daytime and Nighttime SBP

End point title	Change in Average Daytime and Nighttime SBP

End point description:

Blood pressure was measured by 24-hour ABPM. Daytime average SBP was measured from 06:00 to 21:59. Nighttime average SBP was measured from 22:00 to 05:59. The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	30		
Units: mm Hg				
least squares mean (confidence interval 95%)				
Daytime Average	-4.5 (-9.0 to -0.1)	-2.5 (-6.3 to 1.4)		
Nighttime Average	-4.6 (-9.9 to 0.6)	-3.0 (-7.5 to 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hemoglobin HbA1c for Patients With HbA1c ≥5.7% at Baseline

End point title	Change in Hemoglobin HbA1c for Patients With HbA1c ≥5.7% at Baseline

End point description:

The analysis population was patients in the ITT Population who had DM/IGT with HbA1c ≥5.7% at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	36		
Units: Percentage				
least squares mean (confidence interval 95%)	-0.29 (-0.49 to -0.09)	0.00 (-0.17 to 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HbA1c for Patients With HbA1c ≥6.5% at Baseline

End point title	Change in HbA1c for Patients With HbA1c ≥6.5% at Baseline

End point description:

The analysis population was patients in the ITT Population who had DM/IGT with HbA1c ≥6.5% at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	17		
Units: Percentage				
least squares mean (confidence interval 95%)	-0.57 (-1.00 to -0.14)	-0.19 (-0.52 to 0.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With DM Who Achieved 2-hour oGTT Glucose <140 mg/dL

End point title	Number of Patients With DM Who Achieved 2-hour oGTT Glucose <140 mg/dL

End point description:

Glucose was measured using the 2 hour timepoint of the 2-hour oGTT. The analysis population was patients in the ITT Population who had DM with or without HTN at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

2 hours post glucose drink at Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: Patients	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With IGT Who Achieved 2-hour oGTT Glucose <140 mg/dL

End point title	Number of Patients With IGT Who Achieved 2-hour oGTT Glucose <140 mg/dL

End point description:

Glucose was measured using the 2 hour timepoint of the 2-hour oGTT. The analysis population was patients in the ITT Population who had IGT with or without HTN at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

2 hours post glucose drink at Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: Patients	6	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Any Dose Decrease in Antihypertensive Medication

End point title	Number of Patients With Any Dose Decrease in Antihypertensive Medication

End point description:

The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline, received antihypertension medication both at Baseline and postbaseline, and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	33		
Units: Patients	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Any Dose Decrease in Diabetes Medication

End point title	Number of Patients With Any Dose Decrease in Diabetes Medication

End point description:

The analysis population was patients in the ITT Population who had DM/IGT at Baseline, received diabetes medication both at Baseline and postbaseline, and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	25		
Units: Patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Any Dose Increase or Switch in Antihypertensive Medication

End point title	Number of Patients With Any Dose Increase or Switch in Antihypertensive Medication

End point description:

The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline, received antihypertension medication both at Baseline and postbaseline, and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	33		
Units: Patients	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Any Dose Increase or Switch in Diabetes Medication

End point title	Number of Patients With Any Dose Increase or Switch in Diabetes Medication

End point description:

The analysis population was patients in the ITT Population who had DM/IGT at Baseline, received diabetes medication both at Baseline and postbaseline, and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	25		
Units: Patients	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With HbA1c ≥6.5% at Baseline Who Achieved HbA1c <6.5%

End point title	Number of Patients With HbA1c ≥6.5% at Baseline Who Achieved HbA1c <6.5%

End point description:

The analysis population was patients in the ITT Population who had DM with HbA1c ≥6.5% at Baseline and had an available assessment at Week 22.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	21		
Units: Patients	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Normalization of the 24-hour Average SBP (<130 mm Hg)

End point title	Number of Patients With Normalization of the 24-hour Average SBP (<130 mm Hg)

End point description:

Blood pressure was measured by 24-hour ABPM Test. Reported is the number of patients with HTN at Baseline who achieved SBP <130 mm Hg at Week 22. The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: Patients	9	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With a Reduction in 24-hour Average SBP by ≥5 mm Hg

End point title	Number of Patients With a Reduction in 24-hour Average SBP by ≥5 mm Hg

End point description:

Blood pressure was measured by 24-hour ABPM. Reported is the number of patients with HTN at Baseline who achieved at least a 5 mm Hg reduction in 24-hour average SBP at Week 22. The analysis population was patients in the ITT Population who had HTN with or without DM/IGT at Baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 22

End point values	Relacorilant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: Patients	10	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Week 26	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Relacorilant
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	Placebo
Reporting group description:	
Patients will receive placebo matched to study drug once daily.	

Serious adverse events	Relacorilant	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 68 (22.06%)	4 / 69 (5.80%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acral lentiginous melanoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	2 / 68 (2.94%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 68 (1.47%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 68 (2.94%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localized infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Relacorilant	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 68 (95.59%)	60 / 69 (86.96%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 68 (4.41%)	9 / 69 (13.04%)	
occurrences (all)	3	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 68 (14.71%)	4 / 69 (5.80%)	
occurrences (all)	11	4	
Headache			
subjects affected / exposed	7 / 68 (10.29%)	12 / 69 (17.39%)	
occurrences (all)	7	24	
Sciatica			
subjects affected / exposed	5 / 68 (7.35%)	1 / 69 (1.45%)	
occurrences (all)	5	1	
Hypoaesthesia			
subjects affected / exposed	4 / 68 (5.88%)	0 / 69 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 68 (23.53%)	10 / 69 (14.49%)	
occurrences (all)	21	11	
Asthenia			
subjects affected / exposed	8 / 68 (11.76%)	6 / 69 (8.70%)	
occurrences (all)	10	6	
Oedema peripheral			
subjects affected / exposed	6 / 68 (8.82%)	5 / 69 (7.25%)	
occurrences (all)	7	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 68 (7.35%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	14 / 68 (20.59%)	3 / 69 (4.35%)	
occurrences (all)	18	4	
Nausea			
subjects affected / exposed	13 / 68 (19.12%)	8 / 69 (11.59%)	
occurrences (all)	17	10	
Abdominal pain			
subjects affected / exposed	12 / 68 (17.65%)	2 / 69 (2.90%)	
occurrences (all)	15	3	
Diarrhoea			
subjects affected / exposed	9 / 68 (13.24%)	6 / 69 (8.70%)	
occurrences (all)	10	11	
Vomiting			
subjects affected / exposed	6 / 68 (8.82%)	2 / 69 (2.90%)	
occurrences (all)	8	3	
Constipation			
subjects affected / exposed	4 / 68 (5.88%)	1 / 69 (1.45%)	
occurrences (all)	4	1	
Dyspepsia			
subjects affected / exposed	4 / 68 (5.88%)	2 / 69 (2.90%)	
occurrences (all)	4	4	
Abdominal discomfort			
subjects affected / exposed	3 / 68 (4.41%)	4 / 69 (5.80%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 68 (7.35%)	3 / 69 (4.35%)	
occurrences (all)	7	3	
Dyspnoea			
subjects affected / exposed	5 / 68 (7.35%)	2 / 69 (2.90%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 68 (7.35%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Rash			

subjects affected / exposed	5 / 68 (7.35%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Hyperhidrosis			
subjects affected / exposed	4 / 68 (5.88%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 68 (8.82%)	4 / 69 (5.80%)	
occurrences (all)	6	4	
Anxiety			
subjects affected / exposed	0 / 68 (0.00%)	4 / 69 (5.80%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	21 / 68 (30.88%)	9 / 69 (13.04%)	
occurrences (all)	30	9	
Pain in extremity			
subjects affected / exposed	13 / 68 (19.12%)	5 / 69 (7.25%)	
occurrences (all)	18	5	
Arthralgia			
subjects affected / exposed	8 / 68 (11.76%)	14 / 69 (20.29%)	
occurrences (all)	10	16	
Muscle spasms			
subjects affected / exposed	7 / 68 (10.29%)	3 / 69 (4.35%)	
occurrences (all)	8	3	
Myalgia			
subjects affected / exposed	7 / 68 (10.29%)	4 / 69 (5.80%)	
occurrences (all)	7	4	
Musculoskeletal pain			
subjects affected / exposed	2 / 68 (2.94%)	4 / 69 (5.80%)	
occurrences (all)	5	7	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 68 (1.47%)	4 / 69 (5.80%)	
occurrences (all)	1	4	
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 4 / 68 (5.88%) 4 4 / 68 (5.88%) 4	 9 / 69 (13.04%) 9 2 / 69 (2.90%) 2	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 8 / 68 (11.76%) 8	 0 / 69 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2021	1. Revised the conditions under which dose escalation based on tolerability and improvement in hyperglycemia and/or hypertension will occur. 2. Provided conditions for study procedures due to COVID-19 restrictions. 3. Secondary end points for patients with systolic hypertension were added. 4. Exploratory efficacy end points of insulin resistance indices and hyperglucagonemia were added. 5. Added exclusion criteria to exclude candidates who have DM Type 1 or require inhaled glucocorticoid use and have no alternative option or have a history of cyclic Cushing syndrome with fluctuating clinical manifestations or have used mitotane prior to Baseline.
21 June 2023	1. Food effects study data was updated. 2. Secondary and exploratory objectives and end points were revised. 3. Assessment of PK was moved from a secondary to exploratory objective to align with the unchanged placement of PK as an exploratory end point. 4. Reference to mean SBP was revised to average SBP based on 24-hour ABPM for clarity, including primary and secondary end points and inclusion criterion #5 and exclusion criterion #1. 5. Reference to mean DBP was revised to average DBP based on 24-hour ABPM for clarity, including secondary end points and exclusion criterion #1. 6. Removed assessment of clinical benefit as a determinant for inclusion in the extension study. Investigators cannot be expected to assess clinical benefit while blinded. 7. Added unit for glomerular filtration rate to exclusion criterion #5, which was inadvertently omitted and updated section number for exclusion criterion #18. 8. Typo for dose escalation was corrected ("AND" to "OR"). 9. Conditions for use of rescue antidiabetic and antihypertensive concomitant medications were revised for accuracy. 9. Conditions for use of rescue antidiabetic and antihypertensive concomitant medication were revised. 10. Visit windows were revised for clarity, and procedures for visit assessments during dose escalation and maintenance phase were added. 11. Procedures for collection, documentation, and reporting of AEs and SAEs were revised for clarity. 12. The statistical section was revised for alignment with the statistical analysis plan, including analysis of primary, secondary, and exploratory end points.

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.

One protocol amendment occurred after the end of trial date and included updates to primary and secondary end points and statistical analyses. This amendment is not included in the Substantial Protocol Amendments (Globally).

Notes: