Clinical trial results:
A Double-blind, Placebo-Controlled, Randomized Withdrawal Following Open-label Therapy Study to Assess the Safety and Efficacy of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Summary

EudraCT number	2017-001219-35
Trial protocol	ES FR BG HU PL NL DK GR IT RO
Global end of trial date	31 August 2020

Results information

Result version number	v1 (current)
This version publication date	06 February 2022
First version publication date	06 February 2022

Trial information

Trial identification

Sponsor protocol code	COR-2017-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03277690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cortendo AB
Sponsor organisation address	900 Northbrook Drive, Suite 200, Trevose, United States, 19053
Public contact	Clinical Trial Information, Cortendo AB, info@cortendo.com
Scientific contact	Clinical Trial Information, Cortendo AB, info@cortendo.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	20 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of withdrawing to placebo versus continuing treatment with levoketoconazole on the cortisol therapeutic response previously established during open-label levoketoconazole therapy.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and the Guideline for ICH GCP (ICH E6). It also complies with the obligations and requirements of clinical investigators and all other requirements listed in 21 Code of Federal Regulations (CFR) 312. The investigators conducted all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities as well as the study procedures provided by Cortendo AB (also referred to as Cortendo). The specific measures taken to protect subjects during the use of placebo was use of early rescue therapy. Early rescue was a key safety component of the study design that was intended to protect subjects from experiencing disease-related morbidity should they experience a documented loss of therapeutic effect at any time during the Randomized-withdrawal phase. Early rescue during the Randomized-withdrawal phase was to be considered after randomization when a subject demonstrated relapse of hypercortisolemia (i.e., loss of therapeutic response), defined as mUFC from 3 urine collections that is above 1.5× ULN mUFC from 3 urine collections that was above 1× ULN at baseline (RW0) and increases by more than 40% above the baseline value for SONICS-completer cohort subjects only. Other criteria for early rescue were specified in the protocol but were not needed, as all subjects requiring early rescue met this UFC criterion.

Background therapy:

None. All treatments for Cushing's syndrome must have been washed out prior to or during the Screening period in order to qualify for dosing.

Evidence for comparator:

A placebo comparator was used during the 8 week randomized-withdrawal phase of the study. Placebo administration was considered a priori as likely be ineffective to maintain cortisol normalization. Withdrawal to an active comparator was not considered as a practical matter, in that testing for superiority or non-inferiority to an active comparator would require a very large study size beyond the ability to recruit within a reasonable timeframe. Because of its efficiency, the randomized withdrawal design exposes a small number of subjects to placebo compared with most other designs. As an additional protection, subjects were to be provided early rescue therapy with open-label treatment at any time prior to the completion of the Randomized Withdrawal phase if the Investigator determined such rescue was needed based on pre-defined criteria (described in "Protection of trial subjects").

Actual start date of recruitment	15 September 2017
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: 2
Country: Number of subjects enrolled	Poland: 2

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	84
EEA total number of subjects	59

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)	77
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screened: 172
Screen Failures 100
95 Failed Inclusion Criteria (80 INCL04, 3 INCL05, 1 INCL06, 12 INCL11)
5 Met Exclusion Criteria (1 EXCL09, 1 EXCL15, 1 EXCL22, 1 EXCL29, 1 EXCL32)

Period 1

Period 1 title	Dose Titration and Maintenance
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Levoketoconazole

Arm description:

Levoketoconazole tablets 150 mg strength, open-label to be titrated to therapeutic dose

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole, normocort
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablets administered once or twice daily. Individualized dose. Dose range from 150 mg once daily to 1200 mg daily administered as 600 mg twice daily.

Number of subjects in period 1	Levoketoconazole
Started	79
Completed	39
Not completed	40
Consent withdrawn by subject	8
Physician decision	1
Adverse event, non-fatal	15
Sponsor decision - Randomization closed	4
Lack of efficacy	9
Protocol deviation	3

Period 2

Period 2 title	Randomized withdrawal
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

Active and placebo tablets matching in appearance provided to to study investigators for dispensing. Randomization controlled using interactive response system.

Arms

Are arms mutually exclusive?	Yes
Arm title	Levoketoconazole

Arm description:

Levoketoconazole, 150 mg tablets, blinded to identity of ingredients

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole, normocort
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablets administered once or twice daily. Individualized dose. Dose range from 150 mg once daily to 1200 mg daily administered as 600 mg twice daily.

Arm title	Placebo

Arm description:

Placebo tablets identical to levoketoconazole tablets. Ingredients blinded to identity.

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

Dosage and administration details:

Direct substitution for levoketoconazole regimen in RW phase without titration (ie withdrawal to placebo). Also added to existing blinded levoketoconazole regimen in Restoration using rapid titration to restore prior-established therapeutic dose (double dummy).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Three baseline periods were pre-defined but the registry provides for only 1 baseline period. The baseline period associated with the primary endpoint is Period 2 (Randomized-withdrawal.

Number of subjects in period 2[2]	Levoketoconazole	Placebo
Started	21	18
Completed	21	22
Not completed	1	0
Consent withdrawn by subject	1	-

Joined	1	4
SONICS-completer randomized directly	1	4

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: As noted the total number of subjects enrolled is the number enrolled in Dose Titration and Maintenance plus the number directly randomized = 79+5 = 84.

Period 3

Period 3 title	Restoration
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

Blinding was limited to subjects who did not require open-label early rescue during RWW and was accomplished with a "double dummy," whereby the RW drug assignment determined the addition of placebo or active drug in Restoration, such that all subjects received active therapy at their prior-determined therapeutic dose in Restoration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects previously assigned to receive placebo during the RW phase received active therapy in Restoration. 21 of 22 received open-label levoketoconazole as early rescue and rapidly titrated to their therapeutic dose regimen; 1 of 22 received blinded placebo (continued from RW) + blinded levoketoconazole (newly added). The addition of blinded levoketoconazole used rapid titration to return the subject to their prior-established therapeutic dose of levoketoconazole.

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole, normocort
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablets administered once or twice daily. Individualized dose. Dose range from 150 mg once daily to 1200 mg daily administered as 600 mg twice daily.

Arm title	Levoketoconazole

Arm description:

Subjects previously assigned to receive levoketoconazole during the RW phase continued to receive active therapy in Restoration. 4 of 21 received open-label levoketoconazole as early rescue and rapidly titrated to their therapeutic dose regimen; 17 of 22 received blinded levoketoconazole + blinded placebo (newly added). The addition of blinded placebo used the same rapid titration to emulate their prior-established therapeutic dose of levoketoconazole.

Arm type	Experimental
Investigational medicinal product name	Levoketoconazole
Investigational medicinal product code	COR-003
Other name	2S,4R-ketoconazole, normocort
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablets administered once or twice daily. Individualized dose. Dose range from 150 mg once daily to 1200 mg daily administered as 600 mg twice daily.

Number of subjects in period 3	Placebo	Levoketoconazole
Started	22	21
Completed	22	21

Baseline characteristics

Reporting groups	
Reporting group title	Levoketoconazole
Reporting group description:	
Levoketoconazole, 150 mg tablets, blinded to identity of ingredients	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets identical to levoketoconazole tablets. Ingredients blinded to identity.	

Reporting group values	Levoketoconazole	Placebo	Total
Number of subjects	22	22	44
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	45.0	43.6	
standard deviation	± 11.97	± 10.96	-
Gender categorical			
Units: Subjects			
Female	15	19	34
Male	7	3	10
Using antihypertensive medication			
Using at least 1 antihypertensive medication, a proxy for diagnosis of hypertension			
Units: Subjects			
Yes	16	14	30
No	6	8	14
Using antidiabetic medication			
Receiving 1 or more antidiabetic medication, a proxy for diagnosis of diabetes			
Units: Subjects			
Yes	8	6	14
No	14	16	30
Etiology of CS			
Anatomical etiology of endogenous Cushing's syndrome			
Units: Subjects			
Cushing's disease	18	20	38
Ectopic ACTH secretion	0	0	0
Adrenal-dependent	3	1	4

Unknown	1	1	2

Mean UFC (mUFC)			
Mean UFC represents the average of 24-hour UFC measured from nominally 3 adequate 24-hour urine collections. The assay ULN was 138 nmol/24 hours.			
Units: nmol/24 hours			
arithmetic mean	738.69	411.59	
standard deviation	± 1067.025	± 436.176	-

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is comprised of the 84 unique subjects who received at least 1 dose of levoketoconazole in any of the 3 study phases. Baseline for the safety population varies by cohort. For the levoketoconazole-naive cohort, baseline is the latest observation prior to the date of first receiving levoketoconazole in the Dose Titration-maintenance phase (N=79). For the SONICS-completer cohort (N=5), baseline is the latest observation prior to the date of receiving drug in the Randomized-withdrawal phase.

Reporting group values	Safety population		
Number of subjects	84		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	44.7		
standard deviation	± 12.74		
Gender categorical Units: Subjects			
Female	64		
Male	20		
Using antihypertensive medication			
Using at least 1 antihypertensive medication, a proxy for diagnosis of hypertension			
Units: Subjects			
Yes	59		
No	25		
Using antidiabetic medication			
Receiving 1 or more antidiabetic medication, a proxy for diagnosis of diabetes			
Units: Subjects			

Yes	33		
No	51		
Etiology of CS			
Anatomical etiology of endogenous Cushing's syndrome			
Units: Subjects			
Cushing's disease	70		
Ectopic ACTH secretion	2		
Adrenal-dependent	8		
Unknown	4		
Mean UFC (mUFC)			
Mean UFC represents the average of 24-hour UFC measured from nominally 3 adequate 24-hour urine collections. The assay ULN was 138 nmol/24 hours.			
Units: nmol/24 hours			
arithmetic mean	746.73		
standard deviation	± 916.348		

End points

End points reporting groups

Reporting group title	Levoketoconazole
Reporting group description:	
Levoketoconazole tablets 150 mg strength, open-label to be titrated to therapeutic dose	

Reporting group title	Levoketoconazole
Reporting group description:	
Levoketoconazole, 150 mg tablets, blinded to identity of ingredients	

Reporting group title	Placebo
Reporting group description:	
Placebo tablets identical to levoketoconazole tablets. Ingredients blinded to identity.	

Reporting group title	Placebo
Reporting group description:	
Subjects previously assigned to receive placebo during the RW phase received active therapy in Restoration. 21 of 22 received open-label levoketoconazole as early rescue and rapidly titrated to their therapeutic dose regimen; 1 of 22 received blinded placebo (continued from RW) + blinded levoketoconazole (newly added). The addition of blinded levoketoconazole used rapid titration to return the subject to their prior-established therapeutic dose of levoketoconazole.	

Reporting group title	Levoketoconazole
Reporting group description:	
Subjects previously assigned to receive levoketoconazole during the RW phase continued to receive active therapy in Restoration. 4 of 21 received open-label levoketoconazole as early rescue and rapidly titrated to their therapeutic dose regimen; 17 of 22 received blinded levoketoconazole + blinded placebo (newly added). The addition of blinded placebo used the same rapid titration to emulate their prior-established therapeutic dose of levoketoconazole.	

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population is comprised of the 84 unique subjects who received at least 1 dose of levoketoconazole in any of the 3 study phases. Baseline for the safety population varies by cohort. For the levoketoconazole-naive cohort, baseline is the latest observation prior to the date of first receiving levoketoconazole in the Dose Titration-maintenance phase (N=79). For the SONICS-completer cohort (N=5), baseline is the latest observation prior to the date of receiving drug in the Randomized-withdrawal phase.	

Primary: Loss of Therapeutic Response

End point title	Loss of Therapeutic Response
End point description:	
Proportion of subjects with loss of therapeutic response to levoketoconazole upon withdrawing to placebo compared with the proportion of subjects with loss of therapeutic response upon continuing treatment with levoketoconazole. Loss of therapeutic response (i.e., relapse) is inferred based on mUFC from three 24-hour urinary free cortisol (UFC) measurements obtained at any visit from second through final Randomized-withdrawal phase visits (RW1 through RW5 inclusive) when: (1) mUFC is above 1.5× the ULN of the central laboratory's reference range, OR (2) mUFC is more than 40% above the baseline (RW0) value, if the RW0 value is above the ULN (i.e., >1.0× ULN) , OR (3) an early rescue criterion is met.	

End point type	Primary
End point timeframe:	
Up to 8 weeks	

End point values	Levoketoconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: proportion				
Proportion with loss of therapeutic response	9	21		

Statistical analyses

Statistical analysis title	Primary Analysis Method of the Primary Endpoint

Statistical analysis description:

Statistical significance testing was conducted using a logistic regression model containing fixed-effect terms for treatment group (levoketoconazole, placebo) and subject cohort. The results including the estimated proportion and standard error for each treatment group, the estimated difference and standard error (SE) between the 2 treatment groups, and associated 95% CI and p value were derived from the model.

Comparison groups	Levoketoconazole v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Mean difference (net)
Point estimate	-96.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99.4
upper limit	-93.3
Variability estimate	Standard error of the mean
Dispersion value	1.54

Notes:

[1] - Although the logistic regression model was chosen a priori as the primary analysis method, the secondary analysis method is considered to provide the more definitive estimate of treatment efficacy. This is because of the imbalance of cohorts between treatment and placebo groups, resulting in 4 of the 5 subjects in the SONICS-completer cohort being randomized to placebo, all of whom had loss of therapeutic response.

Statistical analysis title	Secondary Analysis Method of Primary Endpoint

Statistical analysis description:

Fisher's Exact Test

Comparison groups	Levoketoconazole v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0002
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	-54.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-75.7
upper limit	-27.4
Variability estimate	Standard error of the mean
Dispersion value	11.38

Notes:

[2] - A supportive analysis that did not require statistical modeling was conducted to confirm the results of the primary analysis. The proportions between the treatment groups were compared using a 2-sided Fisher's Exact test and an exact unconditional two-sided 95% CI of the difference was calculated. Due to imbalance in the fixed effects for the logistic regression model, the Fischer's Exact Test results are considered the more definitive estimate of treatment effect.

Secondary: Normalization of mUFC

End point title	Normalization of mUFC

End point description:

Proportion of subjects with normalization of mUFC at the end of Randomized-withdrawal phase

End point type	Secondary

End point timeframe:

Up to 8 weeks

End point values	Levoketoconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Proportion				
Proportion with mUFC normalization	11	1		

Statistical analyses

Statistical analysis title	Analysis of mUFC normalization

Statistical analysis description:

Inferences derived from secondary efficacy analyses were gated on results from the primary efficacy analysis. Secondary efficacy analyses were hierarchically structured to ensure control of the familywise type I error rate at the 0.05 level. Hypothesis tests for secondary efficacy endpoints were based on null hypotheses that assumed no a priori differences between placebo and levoketoconazole treatments.

Comparison groups	Placebo v Levoketoconazole
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0015
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	45.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	19.2
upper limit	67.9
Variability estimate	Standard error of the mean
Dispersion value	11.55

Notes:

[3] - The proportions of subjects with normalization of mUFC at the end of Randomized-withdrawal phase were compared between treatment groups using Fisher’s Exact test.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During study conduct after receipt of at least 1 dose of study drug.

Adverse event reporting additional description:

AEs were regarded as treatment-emergent (TEAE) if started on or after the time of first dose of study drug administration or, if present prior to first dose of study drug, increased in severity or relationship to study drug. Summaries of TEAEs are for the Randomized-withdrawal phase and for all 3 phases combined (the latter levoketoconazole only).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Levoketoconazole

Reporting group description:

Levoketoconazole, 150 mg tablets, blinded to identity of ingredients

Reporting group title	Placebo

Reporting group description:

Placebo tablets identical to levoketoconazole tablets. Ingredients blinded to identity.

Reporting group title	Safety Population

Reporting group description:

The population of subjects that received at least 1 dose of levoketoconazole during the study, all phases combined.

Serious adverse events	Levoketoconazole	Placebo	Safety Population
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	21 / 84 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
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			

Myocardial infarction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Liver disorder			

subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia	Additional description: The safety population includes among the 3 subjects with SAEs of hypokalemia, the 1 subject with a related SAE of hypokalemia in the levoketoconazole group reported during Randomized-withdrawal phase.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
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	Levoketoconazole	Placebo	Safety Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 22 (22.73%)	5 / 22 (22.73%)	66 / 84 (78.57%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	12 / 84 (14.29%)
occurrences (all)	0	0	17
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 22 (13.64%)	1 / 22 (4.55%)	20 / 84 (23.81%)
occurrences (all)	3	1	21
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	19 / 84 (22.62%)
occurrences (all)	2	2	20
Dizziness			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	11 / 84 (13.10%)
occurrences (all)	0	0	12
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	10 / 84 (11.90%)
occurrences (all)	2	1	11
Oedema peripheral			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	6 / 84 (7.14%)
occurrences (all)	0	0	6
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	5 / 84 (5.95%)
occurrences (all)	0	0	7
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	24 / 84 (28.57%)
occurrences (all)	2	1	34
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	12 / 84 (14.29%)
occurrences (all)	1	3	19
Lip Dry			

subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	8 / 84 (9.52%)
occurrences (all)	0	0	8
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	6 / 84 (7.14%)
occurrences (all)	0	0	6
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	5 / 84 (5.95%)
occurrences (all)	0	0	6
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	5 / 84 (5.95%)
occurrences (all)	0	0	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	7 / 84 (8.33%)
occurrences (all)	0	0	8
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	8 / 84 (9.52%)
occurrences (all)	0	0	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	5 / 84 (5.95%)
occurrences (all)	0	0	5
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	8 / 84 (9.52%)
occurrences (all)	0	0	11
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	7 / 84 (8.33%)
occurrences (all)	0	0	7
Myalgia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	5 / 84 (5.95%)
occurrences (all)	0	0	10
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	7 / 84 (8.33%)
occurrences (all)	0	0	7
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	21 / 84 (25.00%)
occurrences (all)	0	0	28
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	10 / 84 (11.90%)
occurrences (all)	0	0	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2017	Added instructions for SONICS-completers who require re-titration. Clarified that subjects who must re-establish their Therapeutic Dose via re-titration (at the outset of the study) may begin re-titration at their current or most recently received dose at the discretion of the Investigator, rather than start at DL1. Made corrections and clarifications to ensure consistency of wording and alignment of information throughout the Protocol Synopsis and Protocol.
21 June 2018	Added additional Information on Adverse Event of Special Interest (QTc Interval, Liver Function Test Abnormalities and Adrenal Insufficiency. Clarified which screening procedures apply to screening subjects. Updated to requirement to include additional safety visits for subjects currently on levoketoconazole requiring re-titrating after TM0 through TM2, dependent on dose escalations.
14 December 2018	Increased the target number of subjects for randomization to 54 with 27 in each treatment group. Clarified that subjects who completed SONICS but are being treated as part of the levoketoconazole-naïve cohort must re-establish their Therapeutic Dose according to the LOGICS definition.
23 September 2019	Clarification and updated wording on the number of potential randomized subjects and sample size determination. The updated text provides a range of target sample sizes from 46 to 54 that are dependent on the withdrawal rate prior to RW4 during the Randomized Withdrawal Phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported