Clinical trial results:
Prospective, single arm, open-label, multicenter, international study to assess the effects of metyrapone in patients with endogenous Cushing's syndrome during a 12-week treatment period followed by an extension period of 24 weeks.

Summary

EudraCT number	2014-000162-22
Trial protocol	DE IT BE ES HU PL RO
Global end of trial date	29 April 2020

Results information

Result version number	v4 (current)
This version publication date	29 March 2022
First version publication date	19 August 2021
Version creation reason	• Correction of full data set correction in the incidence of some Adverse events
Summary attachment (see zip file)	summary CSR PROMPT (Synopsis PROMPT.pdf)

Trial information

Trial identification

Sponsor protocol code	112025-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02297945
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 116160

Notes:

Sponsors

Sponsor organisation name	HRA Pharma
Sponsor organisation address	200 avenue de Paris , Chatillon, France, 92320
Public contact	Regulatory Affairs Department, HRA Pharma Rare Diseases, +33 1 40 33 24 85, a.japp@HRA-PHARMA.COM
Scientific contact	Medical Affairs Department, HRA Pharma Rare Diseases, +33 1 40 33 32 75, m.bostnavaron@HRA-PHARMA.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 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2020
Global end of trial reached?	Yes
Global end of trial date	29 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of metyrapone (MTP) to normalize cortisol levels (mean Urinary Free Cortisol (of three 24hours urine samples) – mUFC) after 12 weeks of treatment in patients with endogenous Cushing’s syndrome (CS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

Metyrapone (MTP), an inhibitor of the 11β-hydroxylase enzyme, blocks cortisol and aldosterone synthesis. MTP is used for the management of patients with endogenous Cushing's syndrome, and as a diagnostic test for ACTH insufficiency and in the differential diagnosis of ACTH-dependent Cushing's syndrome.

Evidence for comparator:

NA

Actual start date of recruitment	14 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	50
EEA total number of subjects	47

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)	43
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Start of trial (first patient) 14 April 2015.
(Last Patient First Visit) 10 June 2019
(Last Patient Last Visit) 29 April 2020

Pre-assignment

Screening details:

55 patients were planned, 50 were enrolled and analysed.

Period 1

Period 1 title	Core Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Arm title	Core Cohort

Arm description:

Single arm, open label, Metyrapone dose titration based on individual patient response and tolerability up to week 12
Dose will be adjusted at least during control visits:
planned at weeks 1,2,3,4,5,8 and 12 (weeks 3 and 5 were optional).

Arm type	Experimental
Investigational medicinal product name	Metyrapone
Investigational medicinal product code	V04CD01.
Other name	METOPIRONE, METOPIRON, METYCOR, CORMETO, CORMETO, METYRAPONE HRA Pharma
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Metyrapone was supplied as 250 mg soft capsules. The maximum dose is 6 g/day divided into 3 to 4 intakes: If the daily dose cannot be divided equally (i.e. in 250 mg increments), the highest dose will be given at night.
Two possible initiation doses were used depending on the severity of hypercortisolism (based on the mUFC levels):
For patients with moderate hypercortisolism, i.e. baseline mUFC levels ≤ 5-fold the ULN: MTP started at 750 mg/day.
For patients with severe hypercortisolism, i.e. baseline mUFC levels > 5-fold the ULN: MTP started at 1,500 mg/day.
Dose titration should be followed until normal UFC level is achieved:
For patients with moderate Cushing’s syndrome who are initiated with MTP 750 mg/day: the daily dose can be decreased or increased by 250 to 500 mg/day.
For patients with severe Cushing’s syndrome who will start with MTP 1500 mg/day: the daily dose can be decreased or increased by 500 to 1000 mg/day.

Number of subjects in period 1	Core Cohort
Started	50
Completed	47
Not completed	3
Physician decision	2
Adverse event, non-fatal	1

Period 2

Period 2 title	Optional extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Arm title	Extension Cohort

Arm description:

The duration of this optional extension period is up to 24 weeks..
After the first treatment period of 12 weeks , patients who achieved/maintained mUFC levels ≤ ULN or with mUFC levels above normal range but not exceeding 2-fold ULN at week 12, were offered to enter in the optional extension period to continue being treated with MTP for 24 additional weeks. Visits were performed at weeks 24 and 36.

Arm type	Experimental
Investigational medicinal product name	Metyrapone
Investigational medicinal product code	V04CD01.
Other name	METOPIRONE, METOPIRON, METYCOR, CORMETO, CORMETO, METYRAPONE HRA Pharma
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose adjustments (up and down titration) were allowed and possible during the entire period according to cortisol level and/or tolerability.
Visits were performed at weeks 24 and 36

Number of subjects in period 2[1]	Extension Cohort
Started	41
Completed	35
Not completed	6
Patient decision	2
Physician decision	1
Adverse event, non-fatal	3

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: At week 12, among the 50 treated patients (43/50) were eligible to enter the 6-month extension period (normal mUFC levels or mUFC levels above normal range but not exceeding 2-fold ULN at week 12). Of these 43 patients, 41 patients entered the extension period as two patients eligible for the extension period declined to continue.

Baseline characteristics

Reporting groups	
Reporting group title	Core Study

Reporting group description: -

Reporting group values	Core Study	Total	
Number of subjects	50	50	
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)	43	43	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
median	47.0		
full range (min-max)	22 to 73	-	
Gender categorical Units: Subjects			
Female	35	35	
Male	15	15	
Race Units: Subjects			
White	50	50	
Black or African American	0	0	
Asian	0	0	
Disease Characteristics Type of Cushing Syndrome Units: Subjects			
Cushing's disease	44	44	
Ectopic ACTH syndrome	5	5	
Adrenal cause	1	1	
Baseline mUFC by categories Units: Subjects			
> ULN; ≤ 2xULN	2	2	
> 2xULN; ≤5xULN	31	31	
> 5xULN	17	17	
Number of patients with prior radiotherapy and/or surgery for CD Units: Subjects			
Prior surgery	25	25	
Prior surgery and radiotherapy	5	5	

Not applicable	20	20	

Baseline mUFC			
N=49 (mITT)			
Units: (nmol/24h)			
arithmetic mean	1041.7		
standard deviation	± 1337.0	-	

Subject analysis sets

Subject analysis set title	Dataset Efficacy Analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

From the 50 patients enrolled and treated, 49 were included in the mITT set. One patient was excluded from mITT as no post baseline evaluation was available for the primary efficacy criterion: UFC.

Subject analysis set title	Dataset Safety Analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who had received at least one dose of Metyrapone

Reporting group values	Dataset Efficacy Analysis set	Dataset Safety Analysis set	
Number of subjects	49	50	
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)	43		
From 65-84 years	6		
85 years and over	0		
Age continuous Units: years			
median	47.0		
full range (min-max)	22 to 73		
Gender categorical Units: Subjects			
Female	34		
Male	15		
Race Units: Subjects			
White	49		
Black or African American	0		
Asian	0		
Disease Characteristics Type of Cushing Syndrome Units: Subjects			

Cushing's disease	44		
Ectopic ACTH syndrome	4		
Adrenal cause	1		
Baseline mUFC by categories Units: Subjects			
> ULN; ≤ 2xULN	2		
> 2xULN; ≤5xULN	31		
> 5xULN	16		
Number of patients with prior radiotherapy and/or surgery for CD Units: Subjects			
Prior surgery		25	
Prior surgery and radiotherapy		5	
Not applicable		20	
Baseline mUFC			
N=49 (mITT)			
Units: (nmol/24h)			
arithmetic mean		1041.7	
standard deviation	±	± 1337.0	

End points

End points reporting groups

Reporting group title	Core Cohort

Reporting group description:

Single arm, open label, Metyrapone dose titration based on individual patient response and tolerability up to week 12
Dose will be adjusted at least during control visits:
planned at weeks 1,2,3,4,5,8 and 12 (weeks 3 and 5 were optional).

Reporting group title	Extension Cohort

Reporting group description:

The duration of this optional extension period is up to 24 weeks..
After the first treatment period of 12 weeks , patients who achieved/maintained mUFC levels ≤ ULN or with mUFC levels above normal range but not exceeding 2-fold ULN at week 12, were offered to enter in the optional extension period to continue being treated with MTP for 24 additional weeks. Visits were performed at weeks 24 and 36.

Subject analysis set title	Dataset Efficacy Analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

From the 50 patients enrolled and treated, 49 were included in the mITT set. One patient was excluded from mITT as no post baseline evaluation was available for the primary efficacy criterion: UFC.

Subject analysis set title	Dataset Safety Analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who had received at least one dose of Metyrapone

Primary: Normalization of 24h-mUFC at week 12

End point title	Normalization of 24h-mUFC at week 12[1]

End point description:

Normalization of 24h-mUFC at week 12 is presented:
In the mITT population of 49 patients, 23 patients normalized 24h mUFC at week 12.

End point type	Primary

End point timeframe:

Week 12

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: A Clopper Pearson 95% CI was done

End point values	Core Cohort	Dataset Efficacy Analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49	49		
Units: subjects	23	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Urinary Free Cortisol

End point title	Mean Urinary Free Cortisol

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[2]			
Units: nmol/24h				
median (full range (min-max))				
Baseline	570.3 (291.0 to 8476.2)			
week12: Change from baseline(%)	-73.5 (-99.5 to 168.1)			
week24: Change from baseline (%)	-72.6 (-99.8 to 52.0)			
week36: Change from baseline (%)	-69.9 (-99.8 to 52.0)			

Notes:

[2] - Missing data:
week 12: N=2
week24: N=9
week 36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first eucortisolemia

End point title	Time to first eucortisolemia

End point description:

mUFC ≤ ULN

End point type	Secondary

End point timeframe:

week 12

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: days				
median (confidence interval 95%)	34.0 (16.0 to 57.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Responders Rate

End point title	Responders Rate

End point description:

patients with mUFC ≤ ULN or patients with mUFC decrease ≥50% from baseline.

End point type	Secondary

End point timeframe:

Week12, week 24, and week36.

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[3]			
Units: subjects				
week12	39			
week24	31			
week36	25			

Notes:

[3] - Missing data:
week12: 2
week24: 9
week36: 14

Statistical analyses

No statistical analyses for this end point

Secondary: Normalization of 24h-mean urinary free cortisol in extension period

End point title	Normalization of 24h-mean urinary free cortisol in extension period

End point description:

The number of patients with normalisation of 24h UFC during the extension period at weeks 24 and 36 are displayed.

End point type	Secondary

End point timeframe:

week 24 and week 36

End point values	Extension Cohort			
Subject group type	Reporting group			
Number of subjects analysed	41[4]			
Units: subjects				
week24	21			
week36	17			

Notes:

[4] - Missing data:
week24: 9
week36: 14

Statistical analyses

No statistical analyses for this end point

Secondary: Morning serum cortisol-2h after MTP dose

End point title	Morning serum cortisol-2h after MTP dose

End point description:

End point type	Secondary

End point timeframe:

Baseline, week24, and week36.

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[5]			
Units: nmol/L				
median (full range (min-max))				
Baseline	578.0 (137 to 1286)			
Week12: Change from baseline (%)	-67.4 (-89.2 to 50.2)			
Week24: Change from baseline(%)	-67.5 (-92.0 to -2.2)			
Weeek36: Change from baseline(%)	-71.20 (-95.2 to 35.2)			

Notes:

[5] - Missing data:
Baseline: N=5
Week12: N=3
Week24: N=11
Week36: N=15

Statistical analyses

No statistical analyses for this end point

Secondary: Salivary Cortisol at 11 p.m.

End point title	Salivary Cortisol at 11 p.m.

End point description:

End point type	Secondary

End point timeframe:

Baseline, week1, week12, and week 36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: nmol/L				
median (full range (min-max))				
Baseline	12.4 (1.2 to 64.7)			
Week1	5.0 (0.4 to 159.0)			
Week12	4.2 (0.8 to 25.9)			
Week36	4.4 (0.4 to 17.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Late night salivary cortisol

End point title	Late night salivary cortisol

End point description:

End point type	Secondary

End point timeframe:

Baseline, week1, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: nmol/L				
median (full range (min-max))				
week1: Change from baseline(%)	-35.7 (-98.9 to 325.0)			
week12: Change from baseline(%)	-55.4 (-98.0 to 138.8)			
week36: Change from baseline(%)	-71.5 (-96.9 to 158.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting glucose

End point title	Fasting glucose

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: mmol/L				
median (full range (min-max))				
Baseline	5.1 (3.9 to 11.3)			
week12: Change from baseline(%)	-5.3 (-51.3 to 27.1)			
week36: Change from baseline(%)	-6.1 (-44.6 to 39.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting Insulin

End point title	Fasting Insulin

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[6]			
Units: pmol/L				
median (full range (min-max))				
Baseline	93.4 (13.9 to 287.8)			
week12: Change from baseline(%)	-8.7 (-72.1 to 195.0)			
week36: Change from baseline(%)	-15.4 (-86.6 to 161.4)			

Notes:

[6] - Missing data:
Baseline: N=3
week12: N=11
week36: N=19

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin A1c (HbA1c)

End point title	Hemoglobin A1c (HbA1c)

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[7]			
Units: percentage				
median (full range (min-max))				
Baseline	5.8 (3.2 to 8.1)			
Week12: Change from baseline(%)	-2.3 (-23.9 to 13.2)			
Week36: Change from baseline(%)	-3.9 (-37.0 to 22.2)			

Notes:

[7] - Missing data:
Baseline: N=2
week12: N=10
week36: N=15

Statistical analyses

No statistical analyses for this end point

Secondary: Total cholesterol

End point title	Total cholesterol

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[8]			
Units: mmol/L				
median (full range (min-max))				
Baseline	5.4 (3.5 to 9.2)			
week12: Change from baseline(%)	-13.5 (-35.9 to 18.4)			
week36: change from baseline(%)	-18.8 (-46.5 to 34.0)			

Notes:

[8] - Missing data:
Baseline: N=1
week12: N=8
week36: N=13

Statistical analyses

No statistical analyses for this end point

Secondary: HDL-Cholesterol

End point title	HDL-Cholesterol

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[9]			
Units: mmol/L				
median (full range (min-max))				
Baseline	1.5 (0.9 to 2.5)			
week12: change from baseline(%)	-16.4 (-51.7 to 12.0)			
week36: Change from baseline (%)	-23.0 (-49.0 to 7.1)			

Notes:

[9] - Missing data:
Baseline: N=1
week12: N=9
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: LDL-Cholesterol

End point title	LDL-Cholesterol

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[10]			
Units: mmol/L				
median (full range (min-max))				
Baseline	3.4 (1.8 to 7.1)			
week12: Change from baseline(%)	-12.4 (-42.2 to 57.9)			
week36: Change from baseline(%)	-11.0 (-57.8 to 63.2)			

Notes:

[10] - Missing data:
Baseline: N=3
week12: N=11
week36: N=18

Statistical analyses

No statistical analyses for this end point

Secondary: Triglycerides

End point title	Triglycerides

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[11]			
Units: mmol/L				
median (full range (min-max))				
Baseline	1.5 (0.5 to 6.6)			
week12: Change from baseline(%)	0.2 (-64.2 to 73.6)			
week36: Change from baseline(%)	3.6 (-61.7 to 93.1)			

Notes:

[11] - Missing data:
Baseline: N=1
week1é: N=9
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure

End point title	Systolic Blood Pressure

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[12]			
Units: mmHg				
median (full range (min-max))				
Baseline	131.8 (87.5 to 172.0)			
Week12: Change from baseline(%)	-3.2 (-18.5 to 30.0)			
Week24: Change from baseline(%)	-0.6 (-23.0 to 35.3)			
Week36: Change from baseline(%)	-2.6 (-33.1 to 26.7)			

Notes:

[12] - Missing data:
Baseline: N=0
Week12: N=3
Week24: N=10
Week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic blood pressure

End point title	Diastolic blood pressure

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[13]			
Units: mmHg				
median (full range (min-max))				
Baseline	85.3 (52.5 to 113.0)			
Week12: Change from baseline(%)	-5.9 (-21.6 to 50.0)			
Week24: Change from baseline(%)	-0.9 (-40.6 to 60.6)			
Week36: Change from baseline(%)	-5.4 (-30.4 to 27.8)			

Notes:

[13] - Missing data:
Baseline: N=0
Week12: N=3
Week24: N=10
Week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Overall evaluation of Cushing's Syndrome clinical signs related to hypercortisolism

End point title	Overall evaluation of Cushing's Syndrome clinical signs related to hypercortisolism

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week4, week12, week24, and week36

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[14]			
Units: subjects				
week4 improvement or normalization	24			

week12 improvement or normalization	31			
week24 improvement or normalization	25			
week36 improvement or normalization	28			

Notes:

[14] - Missing data:
week4: N=3
week12: N=2
week24: N=9
week36: N=13

Statistical analyses

No statistical analyses for this end point

Secondary: Physical Examination – BMI

End point title	Physical Examination – BMI

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[15]			
Units: Kg/m²)				
arithmetic mean (standard deviation)				
Baseline	30.5 (± 7.3)			
week12: Change from baseline	-0.04 (± 1.1)			
week36: Change from baseline	-0.65 (± 2.2)			

Notes:

[15] - Missing data:
Baseline: N=1
week12: N=3
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Physical Examination – Waist circumference

End point title	Physical Examination – Waist circumference

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[16]			
Units: cm				
arithmetic mean (standard deviation)				
Baseline	106.2 (± 14.2)			
week12: Change from baseline	-0.4 (± 9.6)			
week36: Change from baseline	-3.7 (± 7.4)			

Notes:

[16] - Misssing data:
Baseline: N=3
Week12: N=6
Week36: N=16

Statistical analyses

No statistical analyses for this end point

Secondary: Cushing’s Quality of Life

End point title	Cushing’s Quality of Life

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[17]			
Units: --				
arithmetic mean (standard deviation)				
Baseline	41.5 (± 19.4)			
week12: Change from baseline	9.8 (± 13.8)			
week24: Change from baseline	11.3 (± 13.2)			
week36: Change from baseline	10.4 (± 13.1)			

Notes:

[17] - Missing data:
Baseline: N=0
week12: N=3
week24: N=11
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Tuebingen Cushing’s Disease Quality of Life – Total score

End point title	Tuebingen Cushing’s Disease Quality of Life – Total score

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[18]			
Units: ..				
arithmetic mean (standard deviation)				
Baseline	41.0 (± 22.8)			
week12: Change from baseline	-5.3 (± 13.0)			
week24: Change from baseline	-10.4 (± 13.7)			
week36: Change from baseline	-8.7 (± 16.3)			

Notes:

[18] - Missing data:
Baseline: N=0
week12: N=3
week24: N=11
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Tuebingen Cushing’s Disease Quality of Life – Depression subscore

End point title	Tuebingen Cushing’s Disease Quality of Life – Depression subscore

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[19]			
Units: --				
arithmetic mean (standard deviation)				
Baseline	36.3 (± 25.1)			
week12: Change from baseline	-4.8 (± 18.2)			
week24: Change from baseline	-8.4 (± 18.6)			
week36: Change from baseline	-6.7 (± 16.2)			

Notes:

[19] - Missing data:
Baseline: N=0
week12: N=3
week24: N=11
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Tuebingen Cushing's Disease Quality of Life – Sexual Activity subscore

End point title	Tuebingen Cushing's Disease Quality of Life – Sexual Activity subscore

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[20]			
Units: --				
arithmetic mean (standard deviation)				
Baseline	37.5 (± 29.1)			
week12: Change from baseline	-2.5 (± 17.4)			
week24: Change from baseline	-8.6 (± 18.3)			
week36: Change from baseline	-9.38 (± 15.41)			

Notes:

[20] - Missing data:
Baseline: N=4
week12: N=7
week24: N=13
week36: N=16

Statistical analyses

No statistical analyses for this end point

Secondary: Tuebingen Cushing's Disease Quality of Life – Environment subscore

End point title	Tuebingen Cushing's Disease Quality of Life – Environment subscore

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[21]			
Units: --				
arithmetic mean (standard deviation)				
Baseline	39.3 (± 27.3)			
week12: Change from baseline	-3.4 (± 18.2)			
week24: Change from baseline	-8.1 (± 17.2)			
week36: Change from baseline	-8.1 (± 18.4)			

Notes:

[21] - Missing data:
Baseline: N=0
week12: N=3
week24: N=11
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Tuebingen Cushing's Disease Quality of Life – Eating behavior subscore

End point title	Tuebingen Cushing's Disease Quality of Life – Eating behavior subscore

End point description:

End point type	Secondary

End point timeframe:

Baseline, week12, week24, and week36

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50[22]			
Units: --				
arithmetic mean (standard deviation)				
Baseline	45.7 (± 29.7)			
week12: Change from baseline	-13.8 (± 23.0)			
week24: Change from baseline	-22.9 (± 27.5)			
week36: Change from baseline	-13.0 (± 30.9)			

Notes:

[22] - Missing data:
Baseline: N=0
week12: N=3
week24: N=11
week36: N=14

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of treatment

End point title	Duration of treatment

End point description:

End point type	Secondary

End point timeframe:
globally

End point values	Dataset Safety Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: weeks				
arithmetic mean (standard deviation)				
Duration of treatment globally	30.6 (± 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Final MTP dose

End point title	Final MTP dose

End point description:

End point type	Secondary

End point timeframe:
Global

End point values	Dataset Efficacy Analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49[23]			
Units: mg/day				
median (full range (min-max))				
week12	1500.0 (250 to 5500)			
week24	1500.0 (500 to 5750)			
week36	1500.0 (250 to 5750)			

Notes:

[23] - Missing data:
week12: N=2
week24: N=9
week36: N=14

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from when the subject signs the informed consent to the last visit planned in the protocol.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Baseline to week 12

Reporting group description:

All patients are treated for up to 12 weeks with Metyrapone. After the first administration of MTP (750 mg or 1500 mg/day according to baseline UFC levels), the daily dose is adjusted at scheduled times on the basis of UFC and/or morning serum cortisol measurements and tolerability.

Reporting group title	Baseline to week 36

Reporting group description:

Patients were treated for up to 36 weeks with Metyrapone. After the first administration of MTP (750 mg or 1500 mg/day according to baseline UFC levels), the daily dose is adjusted at scheduled times on the basis of UFC and/or morning serum cortisol measurements and tolerability.

Serious adverse events	Baseline to week 12	Baseline to week 36	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 50 (20.00%)	12 / 50 (24.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour recurrent			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			

subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	6 / 50 (12.00%)	6 / 50 (12.00%)	
occurrences causally related to treatment / all	5 / 6	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			

subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Baseline to week 12	Baseline to week 36	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 50 (84.00%)	47 / 50 (94.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 50 (10.00%)	6 / 50 (12.00%)	
occurrences (all)	6	8	

Hypotension			
subjects affected / exposed	2 / 50 (4.00%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 50 (20.00%)	11 / 50 (22.00%)	
occurrences (all)	19	24	
Dizziness			
subjects affected / exposed	6 / 50 (12.00%)	7 / 50 (14.00%)	
occurrences (all)	6	7	
Paraesthesia			
subjects affected / exposed	3 / 50 (6.00%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 50 (18.00%)	13 / 50 (26.00%)	
occurrences (all)	19	32	
Oedema peripheral			
subjects affected / exposed	6 / 50 (12.00%)	6 / 50 (12.00%)	
occurrences (all)	8	9	
Asthenia			
subjects affected / exposed	3 / 50 (6.00%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 50 (32.00%)	19 / 50 (38.00%)	
occurrences (all)	24	30	
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	5 / 50 (10.00%)	
occurrences (all)	4	8	
Dyspepsia			
subjects affected / exposed	3 / 50 (6.00%)	5 / 50 (10.00%)	
occurrences (all)	4	6	
Abdominal pain upper			
subjects affected / exposed	3 / 50 (6.00%)	4 / 50 (8.00%)	
occurrences (all)	3	4	

Abdominal pain			
subjects affected / exposed	2 / 50 (4.00%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 50 (4.00%)	3 / 50 (6.00%)	
occurrences (all)	5	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 50 (10.00%)	6 / 50 (12.00%)	
occurrences (all)	9	12	
Pain in extremity			
subjects affected / exposed	3 / 50 (6.00%)	3 / 50 (6.00%)	
occurrences (all)	4	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 50 (18.00%)	9 / 50 (18.00%)	
occurrences (all)	12	14	
Hypokalaemia			
subjects affected / exposed	3 / 50 (6.00%)	3 / 50 (6.00%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2015	Spain: The protocol has been updated further to German Competent Authorities' comments. This has also been the opportunity to update the protocol as the study will no more take place in the US and some other minor modifications have been done to improve the first version of the document.
07 December 2015	Spain, Italy, Belgium, Hungary, and Germany: Further to the Investigator's meeting and first inclusions in the study, investigators have requested some clarifications on the study protocol notably collection of urinary free cortisol samples at baseline.

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.

Absence of control or placebo arm

Notes: