Clinical trial results:
CORTICO-COP (CORTICOsteroid reduction in COPD) trial

Summary

EudraCT number	2015-003441-26
Trial protocol	DK
Global end of trial date	06 February 2019

Results information

Result version number	v1 (current)
This version publication date	28 December 2020
First version publication date	28 December 2020

Trial information

Trial identification

Sponsor protocol code	Protocol_CORTICO-COP_PSJUJ

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02857842
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	COPTRIN
Sponsor organisation address	Kildegårdsvej 28, Hellerup, Denmark, 2900
Public contact	Pradeesh Sivapalan, MD, PhD, Lungemedicinsk afdeling, Herlev-Gentofte Hospital, 0045 38674215, pradeesh.s@dadlnet.dk
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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	08 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2018
Global end of trial reached?	Yes
Global end of trial date	06 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose is to examine whether we can reduce the accumulated corticosteroid therapy to the individual COPD patient with the aim of reducing the number of corticosteroid-related adverse events.

Protection of trial subjects:

Monitorering safety data, e.g. all adverse events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 318
Worldwide total number of subjects	318
EEA total number of subjects	318

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)	0
From 65 to 84 years	318
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between Aug 3, 2016, and Sept 30, 2018, we screened 1363 patients. Patients were recruited and followed up between August 2016 and January 2019.

Pre-assignment

Screening details:

Eligible participants were patients included within 24h of admission to the participating sites, aged at least 40 years, with known airflow limitation (defined as a postbronchodilator FEV/forced vital capacity [FVC] ratio ≤0·70) and a specialist-verified diagnosis of COPD, who were designated to start on systemic corticosteroids by the respirat

Period 1

Period 1 title	Eosinophil-guided group (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Control group

Arm description:

This group received standard treatment and 5 days of oral corticosteroids.

Arm type	Standard care of 5 days oral corticosteorids
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

All patients recruited for the trial received an initial dose of systemic corticosteroidson day 1, followed by 37·5 mg of prednisolone oral tablet daily in 5 days.

Arm title	Experimental

Arm description:

The eosinophil-guided group were from the second day given 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least 0·3×10 cells per L. On days when the eosinophil count was lower, prednisolone was not administered.

Arm type	Experimental
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

All patients recruited for the trial received an initial dose of systemic corticosteroidson day 1, followed by 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least 0·3 × 10 cells per L. On days with eosinophil counts less than 0·3 × 10 cells per L, systemic corticosteroids were not administered.

Number of subjects in period 1	Control group	Experimental
Started	159	159
Completed	159	159

Baseline characteristics

Reporting groups	
Reporting group title	Control group
Reporting group description:	
This group received standard treatment and 5 days of oral corticosteroids.	
Reporting group title	Experimental
Reporting group description:	
The eosinophil-guided group were from the second day given 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least 0·3×10 cells per L. On days when the eosinophil count was lower, prednisolone was not administered.	

Reporting group values	Control group	Experimental	Total
Number of subjects	159	159	318
Age categorical Units: Subjects			
Age continuous Units: years			
median	75	75	
inter-quartile range (Q1-Q3)	68 to 82	69 to 81	-
Gender categorical Units: Subjects			
Female	89	86	175
Male	70	73	143
Smoking Units: Subjects			
Current	50	54	104
Past	105	103	208
No smoking history	4	2	6
Diabetes Units: Subjects			
Diabetes	15	24	39
No diabetes	144	135	279
Ischaemic heart disease Units: Subjects			
Ischaemic heart disease	15	22	37
No ischaemic heart disease	144	137	281
Essential hypertension Units: Subjects			
Essential hypertension	61	64	125
No essential hypertension	98	95	193
Hypercholesterolaemia Units: Subjects			
Hypercholesterolaemia	19	19	38
No hypercholesterolaemia	140	140	280
Chronic renal failure Units: Subjects			
Chronic renal failure	10	12	22

No chronic renal failure	149	147	296
Heart failure Units: Subjects			
Heart failure	13	17	30
No heart failure	146	142	288
Osteoporosis Units: Subjects			
Osteoporosis	26	33	59
No osteoporosis	133	126	259
Activities of Daily Living Units: Subjects			
Score 1-2	127	123	250
Score 3-5	32	36	68
Long-acting beta2 agonist			
Medication at baseline			
Units: Subjects			
Long-acting beta2 agonist	127	125	252
No long-acting beta2 agonist	32	34	66
Long-acting muscarinic antagonist			
Medication at baseline			
Units: Subjects			
Long-acting muscarinic antagonist	130	118	248
No long-acting muscarinic antagonist	29	41	70
Inhaled corticosteroid			
Medication at baseline			
Units: Subjects			
Inhaled corticosteroid	96	80	176
No inhaled corticosteorid	63	79	142
Prednisolone prescription 2 weeks before recruitment Units: Subjects			
Predisolone prescription	12	8	20
No prednisolone prescription	147	151	298
Maintenance cortícosteorid therapy (≤10 mg) Units: Subjects			
Maintenance therapy	7	10	17
No maintenance therapy	152	149	301
Increased dyspnoea			
Pulmonary function and symptoms at baseline			
Units: Subjects			
Increased dyspnoea	151	146	297
No increased dyspnoea	8	13	21
Increased sputum volume			
Pulmonary function and symptoms at baseline			
Units: Subjects			
Increased sputum volume	34	33	67
No increased sputum volume	125	126	251
Non-invasive ventilation			
Pulmonary function and symptoms at baseline			
Units: Subjects			

Non-invasive ventilation	5	4	9
No non-invasive ventilation	154	155	309
Increased sputum purulence and cough			
Units: Subjects			
Increased sputum purulence and cough	47	45	92
No increased sputum purulence and cough	112	114	226
Body-mass index			
Units: kg/m^2			
median	23.6	24.2	
inter-quartile range (Q1-Q3)	20.3 to 27.9	20.8 to 26.6	-
Pack-year history			
Units: pack-years			
median	48	45	
inter-quartile range (Q1-Q3)	35 to 56	30 to 57	-
COPD assesment test			
Units: numbers			
median	21	21	
inter-quartile range (Q1-Q3)	15 to 26	17 to 26	-
Medical Research Council dyspnoea scale			
Units: number			
median	4	4	
inter-quartile range (Q1-Q3)	3 to 5	3 to 5	-
FEV1			
Units: liter			
median	0.7	0.7	
inter-quartile range (Q1-Q3)	0.5 to 0.9	0.5 to 0.9	-
FVC			
Units: liter			
median	1.6	1.6	
inter-quartile range (Q1-Q3)	1.2 to 2.1	1.2 to 2.1	-
FEV1 (% predicted)			
Units: percent			
median	30	32	
inter-quartile range (Q1-Q3)	23.0 to 40.5	23.0 to 38.5	-
FVC (% predicted)			
Units: percent			
median	57	56	
inter-quartile range (Q1-Q3)	44 to 70	42 to 72	-

End points

End points reporting groups	
Reporting group title	Control group
Reporting group description:	
This group received standard treatment and 5 days of oral corticosteroids.	
Reporting group title	Experimental
Reporting group description:	
The eosinophil-guided group were from the second day given 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least 0·3×10 cells per L. On days when the eosinophil count was lower, prednisolone was not administered.	

Primary: Days alive and out of hospital within 14 days after recruitment	
End point title	Days alive and out of hospital within 14 days after recruitment
End point description:	
Intention-to-treat (n=318)	
End point type	Primary
End point timeframe:	
14 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: days				
median (full range (min-max))	93 (87 to 99)	89 (83 to 96)		

Statistical analyses

Statistical analysis title	T-test
Comparison groups	Control group v Experimental
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)

Secondary: Treatment failure within 30 days	
End point title	Treatment failure within 30 days
End point description:	

End point type	Secondary
End point timeframe:	
30 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: patients	41	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Readmission with acute exacerbation of COPD or death

End point title	Readmission with acute exacerbation of COPD or death
End point description:	

End point type	Secondary
End point timeframe:	
30 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: number				
median (full range (min-max))	27 (0 to 27)	39 (0 to 39)		

Statistical analyses

Statistical analysis title	cox analyiss
Comparison groups	Control group v Experimental
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard

Secondary: New onset of diabetes in patients without diabetes by day 30

End point title	New onset of diabetes in patients without diabetes by day 30
End point description: N = 279	
End point type	Secondary
End point timeframe: 30 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: Patients	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Worsening of diabetes control in the diabetes group at day 30

End point title	Worsening of diabetes control in the diabetes group at day 30
End point description: N = 39	
End point type	Secondary
End point timeframe: 30 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	24		
Units: Patients	10	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Dyspepsia, ulcer complication, or new proton pump inhibitor treatment within 90 days

End point title	Dyspepsia, ulcer complication, or new proton pump inhibitor treatment within 90 days

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: Patients	12	11		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Length of treatment

End point title	Length of treatment

End point description:

Length of corticosteorid treatment

End point type	Other pre-specified

End point timeframe:

5 days

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: days				
median (inter-quartile range (Q1-Q3))	5.0 (5.0 to 5.0)	2.0 (1.0 to 3.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cumulative corticosteorid dose on day 5

End point title	Cumulative corticosteorid dose on day 5

End point description:

End point type	Other pre-specified

End point timeframe:

5 days

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: mg				
median (inter-quartile range (Q1-Q3))	225.2 (222.1 to 228.3)	121.3 (112.7 to 130.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cumulative corticosteorid dose on day 30

End point title	Cumulative corticosteorid dose on day 30

End point description:

End point type	Other pre-specified

End point timeframe:

30 days

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	292.7 (272.2 to 312.7)	173.8 (151.1 to 196.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cumulative corticosteorid dose on day 90

End point title	Cumulative corticosteorid dose on day 90

End point description:

End point type	Other pre-specified

End point timeframe:

90 days

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: mg	159	159		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Days alive and out of hospital within 14 days after recruitment in patients without pneumonia

End point title	Days alive and out of hospital within 14 days after recruitment in patients without pneumonia
End point description: N = 217	
End point type	Other pre-specified
End point timeframe: 14 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: days	103	114		

Statistical analyses

Statistical analysis title	T-test
Comparison groups	Control group v Experimental
Number of subjects included in analysis	318
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.05
Method	t-test, 1-sided
Parameter estimate	Median difference (net)

Other pre-specified: Days alive and out of hospital within 14 days after recruitment in patients with pneumonia

End point title	Days alive and out of hospital within 14 days after recruitment

	in patients with pneumonia
End point description: N = 101	
End point type	Other pre-specified
End point timeframe: 14 days	

End point values	Control group	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	159		
Units: days	45	56		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

7 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Eosinophil-guided group

Reporting group description:

The eosinophil-guided group were from the second day given 37·5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least 0·3×10 cells per L. On days when the eosinophil count was lower, prednisolone was not administered.

Reporting group title	Control group

Reporting group description: -

Serious adverse events	Eosinophil-guided group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 159 (7.55%)	12 / 159 (7.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
cardiac arrest			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
supra ventricular tachycardia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
deep venous thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 33	0 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
dizziness and headache			

subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
prolonged admission			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-invasive ventilation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
prolonged hospitalization			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism in both lungs			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
readmission			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NIV			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non invasiv ventilation			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged length of hospital stay			

subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Eosinophil-guided group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 159 (9.43%)	14 / 159 (8.81%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Cardiac disorders			
Chest pain			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Obstipation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Non-invasive ventilation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Bloody sputum			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Desaturation			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Itching skin			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Fungal skin infection			

subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urineretention			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Fall			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 159 (0.63%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Fever			
subjects affected / exposed	0 / 159 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	0 / 159 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31122894