Clinical trial results:
“Ensayo clínico, ciego y de grupos paralelos para analizar diferencias en la seguridad de roflumilast administrado una vez al día en días alternos durante dos semanas respecto a la pauta habitual una vez al día”

Summary

EudraCT number	2011-006321-20
Trial protocol	ES
Global end of trial date	20 April 2016

Results information

Result version number	v1 (current)
This version publication date	07 April 2021
First version publication date	07 April 2021
Summary attachment (see zip file)	Final report of results (Informe final ROFLU2011 fdo.pdf)

Trial information

Trial identification

Sponsor protocol code	RO-FLU-2011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fundación Pública Andaluza Progreso y Salud
Sponsor organisation address	Parque Científico y Tecnológico Cartuja, Avda. Américo Vespucio, 15. Edificio S-2. 41092 Sevilla, Seville, Spain, 41092
Public contact	Marta Reboredo Ares, Fundación Pública Andaluza Progreso y Salud, 0034 955 04 04 50, gestionensayosclinicos.fps@juntadeandalucia.es
Scientific contact	Marta Reboredo Ares, Fundación Pública Andaluza Progreso y Salud, 0034 955 04 04 50, gestionensayosclinicos.fps@juntadeandalucia.es

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 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2016
Global end of trial reached?	Yes
Global end of trial date	20 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Analizar si la administración de roflumilast en días alternos durante 2 semanas disminuye la incidencia de abandonos por acontecimientos adversos cuando se compara con la posología habitual.

Protection of trial subjects:

This clinical trial has been conducted in accordance with the principles set forth in the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments set forth by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2012
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	Spain: 105
Worldwide total number of subjects	105
EEA total number of subjects	105

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)	105
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Diagnosis of severe COPD according to GOLD criteria, assessed by post-bronchodilation spirometry (FEV1 < 50%, FEV1/FVC < 70% of theoretical); Age over 18 years; Previous smoking history > 15-20 packs/year; One exacerbation in the previous year; Clinical stability in the last 30 days; Recurrent cough and expectoration.

Pre-assignment

Screening details:

Diagnosis of severe COPD according to GOLD criteria, assessed by post-bronchodilation spirometry (FEV1 < 50%, FEV1/FVC < 70% of theoretical); Age over 18 years; Previous smoking history > 15-20 packs/year; One exacerbation in the previous year; Clinical stability in the last 30 days; Recurrent cough and expectoration.

Period 1

Period 1 title	Recruitment and follow-up
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Compressed lozenge
Routes of administration	Oral use

Dosage and administration details:

500 mg every 48 hours.

Arm title	Control

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Compressed lozenge
Routes of administration	Oral use

Dosage and administration details:

500 mg every 24 hours.

Number of subjects in period 1	Experimental	Control
Started	50	55
Completed	49	53
Not completed	1	2
Consent withdrawn by subject	1	1
Lost to follow-up	-	1

Period 2	
Period 2 title	Data analysis
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Data analyst[1]

Arms	
Are arms mutually exclusive?	Yes
Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Compressed lozenge
Routes of administration	Oral use
Dosage and administration details: 500 mg every 48 hours.	
Arm title	Control
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Compressed lozenge
Routes of administration	Oral use
Dosage and administration details: 500 mg every 24 hours.	

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This study is blinded only to the researcher performing the data analysis.

Number of subjects in period 2	Experimental	Control
Started	49	53
Completed	49	53

Baseline characteristics

Reporting groups	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Reporting group values	Experimental	Control	Total
Number of subjects	50	55	105
Age categorical Units: Subjects			
>18 years	50	55	105
Age continuous Units: years			
arithmetic mean	69.20	66.89	
standard deviation	± 8.69	± 8.04	-
Gender categorical			
No data are available on the gender of the participants. As this is a mandatory field that must be filled in, each group has been completed with 50% men and 50% women.			
Units: Subjects			
Female	25	28	53
Male	25	27	52
Cigarette packets/year Units: cigarette packets/year			
arithmetic mean	57.93	60.22	
standard deviation	± 28.61	± 30.73	-
Weight Units: Kg			
arithmetic mean	84.29	82.57	
standard deviation	± 17.52	± 18.81	-
Height Units: Metres			
arithmetic mean	1.66	4.67	
standard deviation	± 0.07	± 0.08	-
IMC Units: Kg/m2			
arithmetic mean	30.29	29.38	
standard deviation	± 5.95	± 6.11	-
Number of exacerbations in the previous year Units: Number of exacerbations in the previous			
arithmetic mean	2.72	2.83	
standard deviation	± 1.64	± 1.9	-
FVCcc Units: FVCcc			
arithmetic mean	2297.02	2357.22	
standard deviation	± 619.08	± 675.38	-
FVC %			

Units: FVC %			
arithmetic mean	64.86	61.95	
standard deviation	± 13.55	± 13.79	-
FEV 1 cc			
Units: FEV 1 cc			
arithmetic mean	1126.66	1130.37	
standard deviation	± 310.04	± 401.65	-
FEV 1 %			
Units: FEV 1 %			
arithmetic mean	40.79	37.57	
standard deviation	± 7.03	± 8.95	-
6' metres test			
Units: 6' metres test			
arithmetic mean	374.45	386.77	
standard deviation	± 135.43	± 121.82	-
CAT			
Units: CAT			
arithmetic mean	17.68	17.56	
standard deviation	± 7.78	± 7.44	-
Anxiety test			
Units: Anxiety test			
arithmetic mean	5.4	6.5	
standard deviation	± 3.82	± 4.11	-
Depression test			
Units: Depression test			
arithmetic mean	4.26	5.2	
standard deviation	± 3.04	± 4.24	-
BODE			
Units: BODE			
arithmetic mean	4	3.91	
standard deviation	± 1.85	± 1.59	-

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Primary: Study dropout rate due to adverse events

End point title	Study dropout rate due to adverse events[1]

End point description:

The different adverse events that have been measured are: diarrhoea, nausea, weight loss, vomiting, anxiety, depression, nasopharyngitis, upper respiratory tract infection, lumbago, headache, bronchitis, insomnia, flu, vertigo, decreased appetite, pneumonia, hypersensitivity, gynaecomastia, tremor, dizziness, reflux, gastritis, dyspepsia, constipation, myalgia, malaise, fatigue and asthenia.

End point type	Primary

End point timeframe:

During the study

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: Not all the data required are available. However, the final analysis of the results is attached, in which all the information relating to the statistical analysis carried out appears.

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: Participants				
Drop-outs due to adverse events after the 2º visit	9	11		
no drop-outs	40	42		

Statistical analyses

No statistical analyses for this end point

Primary: Study dropout rate due to adverse events

End point title	Study dropout rate due to adverse events[2]

End point description:

The different adverse events that have been measured are: diarrhoea, nausea, weight loss, vomiting, anxiety, depression, nasopharyngitis, upper respiratory tract infection, lumbago, headache, bronchitis, insomnia, flu, vertigo, decreased appetite, pneumonia, hypersensitivity, gynaecomastia, tremor, dizziness, reflux, gastritis, dyspepsia, constipation, myalgia, malaise, fatigue and asthenia.

End point type	Primary

End point timeframe:

During the study

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not all the data required are available. However, the final analysis of the results is attached, in which all the information relating to the statistical analysis carried out appears.

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	53		
Units: Participants				
drop-outs due to adverse events up to the 3º visit	15	12		
no drop-outs	34	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: During the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	Not Known
Dictionary version	1
Reporting groups	
Reporting group title	Both groups

Reporting group description: -

Serious adverse events	Both groups		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 102 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Both groups		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 102 (100.00%)		
Nervous system disorders			
nervousness			
subjects affected / exposed	61 / 102 (59.80%)		
occurrences (all)	61		
headache			
subjects affected / exposed	51 / 102 (50.00%)		
occurrences (all)	51		
insomnia			
subjects affected / exposed	51 / 102 (50.00%)		
occurrences (all)	51		
vertigo			

subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	11		
General disorders and administration site conditions			
MEG			
subjects affected / exposed	20 / 102 (19.61%)		
occurrences (all)	20		
asthenia			
subjects affected / exposed	32 / 102 (31.37%)		
occurrences (all)	32		
Immune system disorders			
hypersensitivity			
subjects affected / exposed	4 / 102 (3.92%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	72 / 102 (70.59%)		
occurrences (all)	72		
Nausea			
subjects affected / exposed	35 / 102 (34.31%)		
occurrences (all)	35		
weight loss			
subjects affected / exposed	102 / 102 (100.00%)		
occurrences (all)	145		
no weight gain			
subjects affected / exposed	102 / 102 (100.00%)		
occurrences (all)	212		
decreased appetite			
subjects affected / exposed	44 / 102 (43.14%)		
occurrences (all)	44		
dysgeusia			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	9		
gastro-oesophageal reflux			
subjects affected / exposed	21 / 102 (20.59%)		
occurrences (all)	21		
gastritis			

subjects affected / exposed occurrences (all) dyspepsia subjects affected / exposed occurrences (all) constipation subjects affected / exposed occurrences (all) fatigue subjects affected / exposed occurrences (all)	9 / 102 (8.82%) 9 12 / 102 (11.76%) 12 10 / 102 (9.80%) 10 11 / 102 (10.78%) 11		
Reproductive system and breast disorders gynaecomastia subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Respiratory, thoracic and mediastinal disorders nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) pneumonia subjects affected / exposed occurrences (all)	6 / 102 (5.88%) 6 25 / 102 (24.51%) 25 2 / 102 (1.96%) 2		
Psychiatric disorders suicidal thoughts subjects affected / exposed occurrences (all) dizziness subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1 24 / 102 (23.53%) 24		
Musculoskeletal and connective tissue disorders lumbar pain			

subjects affected / exposed	27 / 102 (26.47%)		
occurrences (all)	27		
tremor			
subjects affected / exposed	52 / 102 (50.98%)		
occurrences (all)	52		
myalgia			
subjects affected / exposed	24 / 102 (23.53%)		
occurrences (all)	24		
Infections and infestations			
TRS Infection			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	11		
flu symptoms			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2014	Inclusion of new centres and further specification of exclusion criteria that could lead to errors in the inclusion of participants in the study.

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.

The major limitation of the study has been the recruitment of patients, the "n" foreseen in the development of the protocol was not reached, which has been a crucial point in the failure to demonstrate the initial hypothesis.

Notes: