



## 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
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#### 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
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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	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
<b>Arm title</b>	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.

<b>Arm title</b>	Control
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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 <sup>[1]</sup>

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Experimental
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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.

<b>Arm title</b>	Control
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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.

<b>Number of subjects in period 2</b>	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 standard deviation	64.86 ± 13.55	61.95 ± 13.79	-
FEV 1 cc Units: FEV 1 cc arithmetic mean standard deviation	1126.66 ± 310.04	1130.37 ± 401.65	-
FEV 1 % Units: FEV 1 % arithmetic mean standard deviation	40.79 ± 7.03	37.57 ± 8.95	-
6' metres test Units: 6' metres test arithmetic mean standard deviation	374.45 ± 135.43	386.77 ± 121.82	-
CAT Units: CAT arithmetic mean standard deviation	17.68 ± 7.78	17.56 ± 7.44	-
Anxiety test Units: Anxiety test arithmetic mean standard deviation	5.4 ± 3.82	6.5 ± 4.11	-
Depression test Units: Depression test arithmetic mean standard deviation	4.26 ± 3.04	5.2 ± 4.24	-
BODE Units: BODE arithmetic mean standard deviation	4 ± 1.85	3.91 ± 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 <sup>[1]</sup>
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 2 <sup>o</sup> 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 <sup>[2]</sup>
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



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End point timeframe:

During the study

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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.

<b>End point values</b>	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 3 <sup>o</sup> visit	15	12		
no drop-outs	34	41		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During the study

Assessment type	Systematic
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### Dictionary used

Dictionary name	Not Known
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Dictionary version	1
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### Reporting groups

Reporting group title	Both groups
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Reporting group description: -

<b>Serious adverse events</b>	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 %

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

subjects affected / exposed occurrences (all)	9 / 102 (8.82%) 9		
dyspepsia subjects affected / exposed occurrences (all)	12 / 102 (11.76%) 12		
constipation subjects affected / exposed occurrences (all)	10 / 102 (9.80%) 10		
fatigue subjects affected / exposed occurrences (all)	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)	6 / 102 (5.88%) 6		
Bronchitis subjects affected / exposed occurrences (all)	25 / 102 (24.51%) 25		
pneumonia subjects affected / exposed occurrences (all)	2 / 102 (1.96%) 2		
Psychiatric disorders suicidal thoughts subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
dizziness subjects affected / exposed occurrences (all)	24 / 102 (23.53%) 24		
Musculoskeletal and connective tissue disorders lumbar pain			

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

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### 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: