



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, gestionensayosclnicos.fps@juntadeandalucia.es |
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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 |
| 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 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 ^[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 2 ^o 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 3 ^o 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 occurrences (all) | 11 / 102 (10.78%) 11 | | |
| General disorders and administration site conditions MEG subjects affected / exposed occurrences (all) asthenia subjects affected / exposed occurrences (all) | 20 / 102 (19.61%) 20 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) Nausea subjects affected / exposed occurrences (all) weight loss subjects affected / exposed occurrences (all) | 72 / 102 (70.59%) 72 35 / 102 (34.31%) 35 102 / 102 (100.00%) 145 | | |
| no weight gain subjects affected / exposed occurrences (all) | 102 / 102 (100.00%) 212 | | |
| decreased appetite subjects affected / exposed occurrences (all) dysgeusia subjects affected / exposed occurrences (all) gastro-oesophageal reflux subjects affected / exposed occurrences (all) gastritis | 44 / 102 (43.14%) 44 9 / 102 (8.82%) 9 21 / 102 (20.59%) 21 | | |

| | | | |
|--|-------------------------|--|--|
| 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:

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: