



Clinical trial results:

A Phase III Placebo-Controlled Trial Of Celecoxib In Genotype Positive Subjects With Familial Adenomatous Polyposis (FAP)

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2006-002228-40 |
| Trial protocol | ES SE IT GB CZ BE DE HU SK BG |
| Global end of trial date | 29 October 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 March 2016 |
| First version publication date | 18 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A3191193 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00585312 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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? | Yes |
| 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 | 10 March 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 October 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of celecoxib versus placebo in the prevention and treatment of colorectal polyps growth in young subjects with FAP.

Primary Objective: To compare the time from randomization to treatment failure for subjects treated with celecoxib versus subjects treated with placebo, where treatment failure is defined as the earliest occurrence of one or more of the following:

- Appearance of greater than or equal to (\geq) 20 polyps at any colonoscopy during the study, or
- Diagnosis of colorectal malignancy

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 2006 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | Sweden: 4 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Hong Kong: 1 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | United States: 64 |
| Worldwide total number of subjects | 106 |
| EEA total number of subjects | 35 |

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) | 44 |
| Adolescents (12-17 years) | 62 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 305 subjects were screened, whereof 106 were randomized into the study, and of whom 101 took at least 1 dose of study drug. The clinical study was conducted in 18 centers across 13 countries: Belgium, Czech Republic, Hong Kong, Hungary, Israel, Italy, Slovakia, South Africa, Spain, Sweden, Ukraine, United Kingdom, and United States.

Pre-assignment

Screening details:

The randomization was to be stratified by center, age (≥ 12 years old versus less than [$<$] 12 years old), and FAP phenotype (negative versus positive). The subjects were randomized 1:1 to one of the 2 treatments celecoxib or placebo.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Celecoxib |

Arm description:

Celecoxib up to a maximum dose of 400 milligram (mg) was given twice daily.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Celecoxib |
| Investigational medicinal product code | SC-58635 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Celecoxib, approximately 16 milligram per kilogram per day (mg/kg/day) adjusted for changes in body weight. Maximum dose was 400 mg twice daily.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Matching placebo

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo matched to Celecoxib.

| Number of subjects in period 1 | Celecoxib | Placebo |
|---------------------------------------|-----------|---------|
| Started | 55 | 51 |
| Treated | 53 | 48 |
| Completed | 4 | 7 |
| Not completed | 51 | 44 |
| Consent withdrawn by subject | 5 | 1 |
| Adverse Event | 3 | - |
| 'Reason not specified ' | 2 | - |
| Study terminated by the sponsor | 34 | 31 |
| Lost to follow-up | 1 | 1 |
| Lack of efficacy | 6 | 11 |

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | Celecoxib |
| Reporting group description: Celecoxib up to a maximum dose of 400 milligram (mg) was given twice daily. | |
| Reporting group title | Placebo |
| Reporting group description: Matching placebo | |

| Reporting group values | Celecoxib | Placebo | Total |
|--|-----------|---------|-------|
| Number of subjects | 55 | 51 | 106 |
| Age categorical Units: Subjects | | | |
| Age continuous | | | |
| The intent-to-treat (ITT) population consisted of all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether the subjects received any study drug or received a different drug from that to which they were randomized. | | | |
| Units: years | | | |
| arithmetic mean | 12.6 | 12.2 | |
| standard deviation | ± 2.2 | ± 1.8 | - |
| Gender categorical Units: Subjects | | | |
| Female | 29 | 28 | 57 |
| Male | 26 | 23 | 49 |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Celecoxib |
| Reporting group description: Celecoxib up to a maximum dose of 400 milligram (mg) was given twice daily. | |
| Reporting group title | Placebo |
| Reporting group description: Matching placebo | |

Primary: Time to Disease Progression

| | |
|--|--|
| End point title | Time to Disease Progression ^[1] |
| End point description: Time to disease progression was defined as the time from randomization to the earliest occurrence of one or more of the following events: 1. Appearance of ≥ 20 polyps (greater than $>$ 2 millimeter [mm] in size) at any colonoscopy during the study (Polyps); or 2. Diagnosis of colorectal malignancy (ColMal). ITT population (N: 106) consisted of all subjects who were randomized and assigned to treatment. Primary outcome measure was met by 7 (Polyp:7,ColMal:0) subjects in the Celecoxib group and 13 (13,0) in the placebo group. Study was early terminated due to low enrollment and lower than expected endpoint rate. No analysis was performed. | |
| End point type | Primary |
| End point timeframe: 5 years | |
| 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: Study was early terminated due to low enrollment and lower than expected endpoint rate. No statistical analysis was performed. | |

| End point values | Celecoxib | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 ^[2] | 13 ^[3] | | |
| Units: years | | | | |
| arithmetic mean (standard deviation) | 2.2 (\pm 1.08) | 1.8 (\pm 1.3) | | |

Notes:

[2] - Subjects who met the primary outcome measure.

[3] - Subjects who met the primary outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

| | |
|---|---------------------------|
| End point title | Time to Treatment Failure |
| End point description: Time to treatment failure was defined as time from randomization to the earliest occurrence of one or more of the following: 1. Appearance of ≥ 20 polyps ($>$ 2 mm in size) at any colonoscopy during the study (Polyps), or 2. | |

Diagnosis of colorectal malignancy (ColMal), or 3. Treatment related dropout (DO). The treatment related dropout was defined as insufficient clinical response, progression of disease, death, adverse event, treatment-related laboratory abnormality, subject no longer willing to participate in study, and other reasons that might be related to treatment as determined by treating physicians in a blind fashion before database release.

ITT population (N: 106) consisted of all subjects who were randomized and assigned to treatment. Secondary outcome measure was met by 14 (Polyp:7, ColMal:0,DO:14) subjects in the Celecoxib and 14 (13,0,12) in the placebo group. Study was early terminated due to low enrollment and lower than expected endpoint rate. No analysis was performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

5 years

| End point values | Celecoxib | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 ^[4] | 14 ^[5] | | |
| Units: years | | | | |
| arithmetic mean (standard deviation) | 2 (± 1.12) | 1.7 (± 1.3) | | |

Notes:

[4] - Subjects who met the primary outcome measure.

[5] - Subjects who met the primary outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Colorectal Polyps

| | |
|-----------------|-----------------------------------|
| End point title | Total Number of Colorectal Polyps |
|-----------------|-----------------------------------|

End point description:

Total number of colorectal polyps >2 mm in size, that were detected over Years 1 - 5 cumulatively.

Weighted total number of colorectal polyps over Years 1 – 5 cumulatively was defined as the total number of colorectal polyps >2 mm in size, that were detected over Years 1 - 5, divided by the number of colonoscopies that the subject had during the study.

ITT population (N: 106) consisted of all subjects who were randomized and assigned to a treatment. Study was early terminated due to low enrollment and lower than expected endpoint rate and no analysis was performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1 to 5

| End point values | Celecoxib | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 51 | | |
| Units: polyps | | | | |
| arithmetic mean (standard deviation) | | | | |
| Year 1 (N: 27, 30) | 3 (± 2.68) | 8.1 (± 7.32) | | |
| Year 2 (N: 21, 25) | 8.8 (± 6.63) | 13.7 (± 10.51) | | |

| | | | | |
|--------------------------------------|----------------|----------------|--|--|
| Year 3 (N: 16, 14) | 13.4 (± 11.31) | 22.3 (± 11.74) | | |
| Year 4 (N: 8, 7) | 18.6 (± 17.65) | 36.4 (± 22.5) | | |
| Year 5 (N: 2, 2) | 30.5 (± 21.92) | 46.5 (± 34.65) | | |
| Years 1 - 5 cumulatively (N: 33, 36) | 4.3 (± 3.58) | 8.6 (± 7.12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Colorectal Polyp Burden

| | |
|-----------------|-------------------------|
| End point title | Colorectal Polyp Burden |
|-----------------|-------------------------|

End point description:

The polyp burden was defined as the sum of the largest diameters of all polyps (>2 mm in size) over Years 1 - 5 cumulatively.

Weighted colorectal polyp burden over Years 1 – 5 cumulatively was defined as the polyp burden over Years 1 - 5 divided by the number of colonoscopies that the subject had during the study.

ITT population (N: 106) consisted of all subjects who were randomized and assigned to a treatment. Study was early terminated due to low enrollment and lower than expected endpoint rate and no analysis was performed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1 to 5

| End point values | Celecoxib | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 51 | | |
| Units: millimeter(s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Year 1 (N: 27, 30) | 4 (± 1.97) | 4.2 (± 2.05) | | |
| Year 2 (N: 21, 25) | 6.9 (± 2.28) | 8.1 (± 4.06) | | |
| Year 3 (N: 16, 14) | 9.6 (± 3.14) | 11.6 (± 4.05) | | |
| Year 4 (N: 8, 7) | 12.9 (± 3.31) | 18.7 (± 5.88) | | |
| Year 5 (N: 2, 2) | 20 (± 7.07) | 20 (± 4.24) | | |
| Year 1 - 5 cumulatively (N: 33, 36) | 4.1 (± 1.68) | 4.3 (± 1.61) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events were reported from randomization through and including 30 calendar days after the last administration of the study drug

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as non serious in another subject, or one subject may have experienced both a serious and non serious event during the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Celecoxib |
|-----------------------|-----------|

Reporting group description:

Celecoxib, approximately 16 mg/kg/day (adjusted for changes in body weight). Maximum dose was 400 mg twice daily.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching placebo.

| Serious adverse events | Celecoxib | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 0 / 48 (0.00%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 48 (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 | Celecoxib | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 36 / 53 (67.92%) | 30 / 48 (62.50%) | |
| Investigations | | | |
| Albumin urine present | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 0 / 48 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 53 (30.19%) | 14 / 48 (29.17%) | |
| occurrences (all) | 60 | 59 | |
| Migraine | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 4 / 48 (8.33%) | |
| occurrences (all) | 2 | 4 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 1 / 48 (2.08%) | |
| occurrences (all) | 7 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 4 / 48 (8.33%) | |
| occurrences (all) | 10 | 4 | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 5 / 48 (10.42%) | |
| occurrences (all) | 2 | 7 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 9 / 53 (16.98%) | 4 / 48 (8.33%) | |
| occurrences (all) | 10 | 4 | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 9 / 53 (16.98%) | 10 / 48 (20.83%) | |
| occurrences (all) | 20 | 22 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 3 / 48 (6.25%) | |
| occurrences (all) | 6 | 3 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 4 / 48 (8.33%) | |
| occurrences (all) | 8 | 6 | |
| Nausea | | | |
| subjects affected / exposed | 8 / 53 (15.09%) | 8 / 48 (16.67%) | |
| occurrences (all) | 14 | 14 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 3 / 48 (6.25%) | |
| occurrences (all) | 6 | 3 | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 53 (16.98%) | 9 / 48 (18.75%) | |
| occurrences (all) | 16 | 14 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 53 (15.09%) | 6 / 48 (12.50%) | |
| occurrences (all) | 10 | 8 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 1 / 48 (2.08%) | |
| occurrences (all) | 5 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 3 / 48 (6.25%) | |
| occurrences (all) | 0 | 4 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 5 / 48 (10.42%) | |
| occurrences (all) | 9 | 5 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 2 / 48 (4.17%) | |
| occurrences (all) | 3 | 3 | |
| Pain in extremity | | | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 53 (3.77%) 2 | 5 / 48 (10.42%) 6 | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 2 / 48 (4.17%) | |
| occurrences (all) | 4 | 2 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 2 / 48 (4.17%) | |
| occurrences (all) | 3 | 4 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 1 / 48 (2.08%) | |
| occurrences (all) | 3 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 1 / 48 (2.08%) | |
| occurrences (all) | 7 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 4 / 48 (8.33%) | |
| occurrences (all) | 7 | 6 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 9 / 48 (18.75%) | |
| occurrences (all) | 4 | 9 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 4 / 48 (8.33%) | |
| occurrences (all) | 0 | 6 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 03 May 2007 | Enhanced renal monitoring and additional AE management sections were added. |
| 17 October 2011 | Change of post-colonoscopy interval pre-randomization from 30 to 90 days, provision for re-screening screen failures, drug-induced liver injury and change of polyp count from 20 to 30 were added. |
| 12 March 2013 | Study discontinuation criteria was updated: If a subject did not return for a scheduled visit, every effort was made to contact the subject. If all efforts to contact the subject, including direct mail, telephone contact, contact through the next of kin, contact through the subject's family physician or neighbors failed, then subject was declared lost-to-follow-up. |

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 study was early terminated on 22 July 2013, due to the low number of subjects and no efficacy analysis was performed. Only descriptive statistics was performed.

Notes: