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:
a. Appearance of greater than or equal to (≥) 20 polyps at any colonoscopy during the study, or
b. 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 (± 1.08)	1.8 (± 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	2 / 53 (3.77%)	5 / 48 (10.42%)	
occurrences (all)	2	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: