Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of the Safety and Tolerability of N–Acetylcysteine in Patients with Idiopathic Pulmonary Fibrosis with Background Treatment of Pirfenidone

Summary

EudraCT number	2012-000564-14
Trial protocol	BE SE DE IT AT GB DK
Global end of trial date	24 February 2015

Results information

Result version number	v1 (current)
This version publication date	30 April 2016
First version publication date	30 April 2016

Trial information

Trial identification

Sponsor protocol code	PIPF-023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02707640
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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?	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	24 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2015
Global end of trial reached?	Yes
Global end of trial date	24 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of treatment with N-acetylcysteine (NAC) (1800 milligram/day [mg/day]) in subjects with mild to moderate idiopathic pulmonary fibrosis (IPF) with background treatment of pirfenidone therapy.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Pirfenidone was an oral administration of a dose of at least 1602 mg/day and no more than 2404 mg/day during the wash-out and screening period and for at least 8 weeks prior to randomisation.

Evidence for comparator: -

Actual start date of recruitment	28 June 2013
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	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Italy: 20
Worldwide total number of subjects	122
EEA total number of subjects	122

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)	40
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening details: A total of 123 subjects were enrolled. Total of 122 subjects received at least 1 dose of double-blind study medication, and thus included in the modified intent-to-treat (mITT) population

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	N–Acetylcysteine (NAC)

Arm description:

Subjects randomised to this arm were administered NAC three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed until 4 weeks after last study treatment dose.

Arm type	Experimental
Investigational medicinal product name	N–Acetylcysteine (NAC)
Investigational medicinal product code	
Other name	Fluimucil
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 600 mg NAC effervescent tablets orally three times a day.

Arm title	Placebo

Arm description:

Subjects randomised to this arm were administered matching placebo orally three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed until 4 weeks after last study treatment dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo to NAC orally three times a day.

Number of subjects in period 1	N–Acetylcysteine (NAC)	Placebo
Started	60	62
Completed	52	55
Not completed	8	7
Adverse event, serious fatal	1	2
Consent withdrawn by subject	-	1
Subject's personal decision	1	2
Adverse event, non-fatal	4	2
Sponsor discretion	1	-
Principal investigator discretion	1	-

Baseline characteristics

Reporting groups	
Reporting group title	N–Acetylcysteine (NAC)
Reporting group description:	
Subjects randomised to this arm were administered NAC three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed until 4 weeks after last study treatment dose.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to this arm were administered matching placebo orally three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed until 4 weeks after last study treatment dose.	

Reporting group values	N–Acetylcysteine (NAC)	Placebo	Total
Number of subjects	60	62	122
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	66.7	67.5	
standard deviation	± 7.99	± 6.22	-
Gender categorical Units: Subjects			
Female	7	11	18
Male	53	51	104

End points

End points reporting groups

Reporting group title	N–Acetylcysteine (NAC)

Reporting group description:

Subjects randomised to this arm were administered NAC three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed until 4 weeks after last study treatment dose.

Reporting group title	Placebo

Reporting group description:

Subjects randomised to this arm were administered matching placebo orally three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed until 4 weeks after last study treatment dose.

Primary: Percentage of Subjects With Dose Reductions

End point title	Percentage of Subjects With Dose Reductions[1]

End point description:

Percentage of subjects with dose reductions in N-Acetylcysteine and placebo cohorts during the 24-week treatment period. mITT population included subjects who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

From baseline up to 24 weeks

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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	5	4.8		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Early Treatment Discontinuations

End point title	Percentage of Subjects with Early Treatment Discontinuations[2]

End point description:

Percentage of subjects with early study treatment discontinuations in N-Acetylcysteine and placebo cohorts during the 24-week treatment period. mITT population included subjects who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

From baseline up to 24 weeks

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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	14.8	11.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs)[3]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject who is administered a study treatment regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, could be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. mITT Population included subjects who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

Until 28 days from last dose of study treatment (Week 28)

Notes:

[3] - 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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	76.7	80.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-Emergent Serious Adverse Events

(SAEs)

End point title	Percentage of Subjects With Treatment-Emergent Serious Adverse Events (SAEs)[4]

End point description:

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose results in death, is life threatening, requires hospitalization or prolongation of hospitalization, or results in disability/incapacity, or congenital anomaly/birth defect. mITT population included subjects who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

Until 28 days from last dose of study treatment (Week 28)

Notes:

[4] - 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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	5	6.5		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Treatment

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events Resulting in Permanent Discontinuation of Study Treatment[5]

End point description:

mITT population included subjects who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

Until 28 days from last dose of study treatment (Week 28)

Notes:

[5] - 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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	6.7	1.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-Emergent Deaths of All Causes

End point title	Percentage of Subjects With Treatment-Emergent Deaths of All Causes[6]

End point description:

mITT population included who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

Until 28 days from last dose of study treatment (Week 28)

Notes:

[6] - 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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	1.7	4.8		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events That Led to Dose Reduction or Temporary Discontinuation of Study Treatment

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events That Led to Dose Reduction or Temporary Discontinuation of Study Treatment[7]

End point description:

mITT population included who received at least 1 dose of double-blind study medication (NAC or placebo).

End point type	Primary

End point timeframe:

Until 28 days from last dose of study treatment (Week 28)

Notes:

[7] - 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: Only descriptive data was planned to be reported.

End point values	N–Acetylcysteine (NAC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of subjects				
number (not applicable)	10	6.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until 28 days from last dose of study treatment (Week 28)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	N–Acetylcysteine (NAC)

Reporting group description:

Subjects randomised to this arm were administered NAC three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed for 4 weeks after last study treatment dose.

Reporting group title	Placebo

Reporting group description:

Subjects randomised to this arm were administered matching placebo orally three times daily and a dose of pirfenidone of at least 1602 mg/day for 24 weeks. Subjects were to be on a dose of pirfenidone of at least 1602 mg/day for a minimum of 8 weeks prior to randomisation and were followed for 4 weeks after last study treatment dose.

Serious adverse events	N–Acetylcysteine (NAC)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 60 (5.00%)	4 / 62 (6.45%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 60 (1.67%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 60 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			

subjects affected / exposed	0 / 60 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 60 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 60 (1.67%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 60 (1.67%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 60 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 62 (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	N–Acetylcysteine (NAC)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 60 (76.67%)	50 / 62 (80.65%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 60 (1.67%)	5 / 62 (8.06%)	
occurrences (all)	1	5	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 60 (6.67%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Diarrhoea			
subjects affected / exposed	6 / 60 (10.00%)	9 / 62 (14.52%)	
occurrences (all)	9	10	
Nausea			
subjects affected / exposed	4 / 60 (6.67%)	5 / 62 (8.06%)	
occurrences (all)	4	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 60 (13.33%)	7 / 62 (11.29%)	
occurrences (all)	8	11	
Dyspnoea			
subjects affected / exposed	3 / 60 (5.00%)	4 / 62 (6.45%)	
occurrences (all)	3	6	
Productive cough			
subjects affected / exposed	3 / 60 (5.00%)	2 / 62 (3.23%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 60 (5.00%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Photosensitivity reaction			
subjects affected / exposed	8 / 60 (13.33%)	1 / 62 (1.61%)	
occurrences (all)	9	1	
Rash			

subjects affected / exposed	2 / 60 (3.33%)	6 / 62 (9.68%)	
occurrences (all)	3	6	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 60 (6.67%)	3 / 62 (4.84%)	
occurrences (all)	4	3	
Influenza			
subjects affected / exposed	3 / 60 (5.00%)	1 / 62 (1.61%)	
occurrences (all)	3	2	
Nasopharyngitis			
subjects affected / exposed	7 / 60 (11.67%)	7 / 62 (11.29%)	
occurrences (all)	7	7	
Upper respiratory tract infection			
subjects affected / exposed	3 / 60 (5.00%)	5 / 62 (8.06%)	
occurrences (all)	3	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2014	Study sample size estimate was reduced from 125 subjects per arm to allow for an observed exposure of approximately 62.5 subject-years per arm to 60 subjects per arm for an observed exposure of approximately 30 subject-years per arm which was considered reasonably long to detect potential differences of the safety and tolerability of NAC added to background treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported