Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Crossover Study to Assess the Effect of 28 Day Treatment with Fostair® pMDI 200/12 on biomarkers of platelet adhesion in Patients with Idiopathic pulmonary fibrosis.

Summary

EudraCT number	2013-004404-19
Trial protocol	GB
Global end of trial date	25 April 2015

Results information

Result version number	v1 (current)
This version publication date	02 January 2019
First version publication date	02 January 2019
Summary attachment (see zip file)	clinical study report (Revised Final Report.docx)

Trial information

Trial identification

Sponsor protocol code	Acadmed18013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02048644
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	hull and east yorkshire nhs hosptals trust
Sponsor organisation address	castle hill hospital, castle rd, cottingham, United Kingdom, hu16 5jq
Public contact	Wright, Hull and East Yorkshire Hospitals NHS Trust , 44 1482624067, c.e.wright@hull.ac.uk
Scientific contact	caroline Wright, Hull and East Yorkshire Hospitals NHS Trust , 44 1482624067, c.e.wright@hull.ac.uk

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	12 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2015
Global end of trial reached?	Yes
Global end of trial date	25 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

There is a significant unmet medical need for the treatment of Idiopathic pulmonary fibrosis (IPF); there is no effective therapy for treatment of IPF in the UK, and only pirfenidone is approved for treatment. The main goal of the current study is to evaluate the effect of Fostair on the biomarkers of platelet activation in IPF disease. We believe that platelets- cell fragments which have a major role in wound healing, also have a pivotal role in the pathogenesis of IPF and whether this translates in to a clinically beneficial effect of Fostair on IPF disease.

The primary objective of this study is to determine the effect of Fostair fine particle Metered dose inhaler on markers of pulmonary fibrosis. Primary endpoint will be a change in biomarkers of platelet activation.

Protection of trial subjects:

continued in routine care

Background therapy: -

Evidence for comparator:

No Comparators used

Actual start date of recruitment	03 March 2014
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	United Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	2
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place within the pulmonary fibrosis clinics and also from the pulmonary fibrosis support group by informing patients of the ongoing studies. recruitment began on 11/06/2014

Pre-assignment

Screening details:

screening patirents were screened for eligibility to take part in the study main criteria were adults (40-85 years of age) with IPF diagnosis according to ATS/ERS Consensus Statement, Able to maintain O2 saturation of ≥ 89% while breathing room air at rest and a FVC (forced vital capacity) of 50-110% predicted value.

Period 1

Period 1 title	baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Arm title	baseline

Arm description:

no treatmentnt

Arm type	baseline
Investigational medicinal product name	no product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

baseline period no products given to subjects as title suggests BASELINE PERIOD

Number of subjects in period 1	baseline
Started	20
Completed	20

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

BDP/Formoterol 100/6 HFA pMDI combination inhaler and matched placebo were packed and supplied by Chiesi Ltd. The inhalers were identical; ensuring both patient and investigator remained blind to the active medication being received

Arms

Are arms mutually exclusive?	No
Arm title	Fostair

Arm description:

Budesonide phosphate (BDP)/Formoterol 100/6 HFA pMDI

Arm type	Experimental
Investigational medicinal product name	budesonide phosphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide phosphate (BDP)/Formoterol 100/6 HFA delivered by metered dose inhaler.
2 puffs BD. total dose budesonide /day 400 mcg

Arm title	placebo

Arm description:

matched placebo metered dose inhalers. The inhalers were identical; to the test inhalers ensuring both patient and investigator blind

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 puffs of placebo twice a day

Number of subjects in period 2	Fostair	placebo
Started	19	19
Completed	19	17
Not completed	0	2
Adverse event, non-fatal	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	baseline
Reporting group description:	
no treatmentnt	

Reporting group values	baseline	Total	
Number of subjects	20	20	
Age categorical			
subject population-patients with diagnosis of IPF			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
patients with Idiopathic pulmonary fibrosis meeting study inclusion/exclusion criteria			
Units: years			
arithmetic mean	71.1		
standard deviation	± 8.7	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	7	7	

End points

End points reporting groups	
Reporting group title	baseline
Reporting group description:	
no treatmentnt	
Reporting group title	Fostair
Reporting group description:	
Budesonide phosphate (BDP)/Formoterol 100/6 HFA pMDI	
Reporting group title	placebo
Reporting group description:	
matched placebo metered dose inhalers. The inhalers were identical; to the test inhalers ensuring both patient and investigator blind	

Primary: p SELECTIN expression	
End point title	p SELECTIN expression
End point description:	
Measured differences between the baseline and two treatments on AUC P-selectin expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.	
End point type	Primary
End point timeframe:	
recorded at baseline, following 4 week Fostair and following 4 week placebo inhalers with a 4week washout between therapy	

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: AUC				
arithmetic mean (standard deviation)	284 (± 124)	197 (± 72)	224 (± 80)	

Statistical analyses

Statistical analysis title	P-selectiin difference from baseline ANOVA
Statistical analysis description:	
measured differences between the baseline and Fostair on AUC P-selectin expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.	
Comparison groups	baseline v Fostair
Number of subjects included in analysis	34
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.8
upper limit	140.6
Variability estimate	Standard deviation

Notes:

[1] - ANOVA and Tukey post hoc test for multiple comparisons.

Statistical analysis title	P-selectin difference from baseline with placebo

Statistical analysis description:

ANOVA and Tukey post hoc test for multiple comparisons.

Comparison groups	baseline v placebo
Number of subjects included in analysis	34
Analysis specification	Post-hoc
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22
upper limit	141
Variability estimate	Standard deviation

Primary: platelet fibrinogen expression

End point title	platelet fibrinogen expression

End point description:

Measured differences between the baseline and two treatments on AUC platelet fibrinogen expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.

End point type	Primary

End point timeframe:

measured at baseline, following 4 weeks Fostair and following 4 weeks placebo with a 4 week washout between treatments

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: AUC				
arithmetic mean (standard deviation)	786 (± 152)	686 (± 188)	769 (± 154)	

Statistical analyses

Statistical analysis title	Platelet fibrinogen expression Fostair

Statistical analysis description:

Measured differences between the baseline and Fostair treatment in AUC platelet-fibrinogen expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.

Comparison groups	Fostair v baseline
Number of subjects included in analysis	34
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53
upper limit	253
Variability estimate	Standard deviation

Notes:

[2] - AUC Platelet fibrinogen expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.
Study was a crossover study thus only 17 patients analysed

Statistical analysis title	platelet fibrinogen expression with placebo

Statistical analysis description:

Measured differences between the baseline and placebo on AUC Platelet fibrinogen expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.

Comparison groups	placebo v baseline
Number of subjects included in analysis	34
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136
upper limit	169
Variability estimate	Standard deviation

Notes:

[3] - AUC P-selectin expression obtained from ANOVA and Tukey post hoc test for multiple comparisons.
the study was a crossover therefore only 17 patients data analysed

Primary: platelet monocyte aggregates

End point title	platelet monocyte aggregates

End point description:

Differences between the baseline and two treatments on AUC platelet monocyte aggregates obtained from ANOVA and Tukey post hoc test for multiple comparisons.

End point type	Primary

End point timeframe:

measured at baseline, following 4 weeks Fostair and following 4 weeks placebo inhalers with a 4 week washout between treatments

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: AUC				
arithmetic mean (standard deviation)	344 (± 130)	330 (± 181)	382 (± 141)	

Statistical analyses

Statistical analysis title	platelet monocyte aggregates Fostair

Statistical analysis description:

differences between the baseline and Fostair on AUC platelet monocyte aggregates (PMA) obtained from ANOVA and Tukey post hoc test for multiple comparisons.

Comparison groups	baseline v Fostair
Number of subjects included in analysis	34
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-117
upper limit	144
Variability estimate	Standard deviation

Notes:

[4] - Change from baseline AUC PMA from ANOVA and Tukey post hoc test for multiple comparisons. This was a crossover study thus 17 patients data analysed

Statistical analysis title	PMA- placebo

Statistical analysis description:

Differences between the baseline and placebo AUC PMA obtained from ANOVA and Tukey post hoc test for multiple comparisons.

Comparison groups	baseline v placebo
Number of subjects included in analysis	34
Analysis specification	Post-hoc
Analysis type	superiority[5]
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-168
upper limit	92.4

Variability estimate	Standard deviation

Notes:

[5] - ANOVA and Tukey post hoc test for multiple comparisons.
This was a crossover study thus 17 patients data analysed

Secondary: Forced expired volume in 1 second

End point title	Forced expired volume in 1 second

End point description:

End point type	Secondary

End point timeframe:

from baseline through to post 4 weeks foster and post 4 weeks placebo.

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17[6]	17[7]	17[8]	
Units: ml				
arithmetic mean (standard deviation)	215 (± 56)	222 (± 58)	215 (± 62)	

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Paired test
Comparison groups	baseline v Fostair v placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Secondary: Forced vital capacity

End point title	Forced vital capacity

End point description:

End point type	Secondary

End point timeframe:

measurement taken at baseline, at 4weeks post foster therapy, and at 4 weeks post placebo therapy.
Each subject acted as own control, crossover study

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: ml				
arithmetic mean (standard deviation)	264 (± 79)	270 (± 74)	268 (± 80)	

Statistical analyses

Statistical analysis title	paired ttest

Statistical analysis description:

change from baseline in FVC following 4 weeks placebo was compared with change in FVC from baseline following 4 weeks fostair

Comparison groups	baseline v Fostair v placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Secondary: FEF25-75

End point title	FEF25-75

End point description:

End point type	Secondary

End point timeframe:

measured at baseline, at 4weeks post placebo and at 4weeks post fostair therapy

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: ml				
arithmetic mean (standard deviation)	240 (± 98)	253 (± 72)	234 (± 84)	

Statistical analyses

Statistical analysis title	paired ttest

Statistical analysis description:

compared change from baseline in FEF 25/75 with placebo with that of change in from baseline following fostair. crossover study

Comparison groups	baseline v Fostair v placebo

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Secondary: FENO

End point title	FENO

End point description:

End point type	Secondary

End point timeframe:

Measured at baseline, following 4 weeks placebo and following 4 weeks treatment with fostair with 4 week interval between treatments

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12[9]	12	12	
Units: PPB				
arithmetic mean (standard deviation)	19 (± 8)	18 (± 7)	18 (± 8)	

Notes:

[9] - Only 12 patients were able to produce sputum at all relevant visits through out study as per protoco

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

compared change from baseline between fostair and placebo

Comparison groups	baseline v Fostair v placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	≤ 0.05 [11]
Method	ANOVA
Parameter estimate	Mean difference (final values)

Notes:

[10] - compared baseline placebo and fostair with bonferoni. within group comparison as each individual acted as own control. only 12 subjects analysed

[11] - a value<0.05 demonstrated significant difference

Secondary: fev1/FVC

End point title	fev1/FVC

End point description:

End point type	Secondary

End point timeframe:

measured at baseline and at 4weeks post placebo and at 4 weeks post fostair with a 4 week interval between treatments.

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17	
Units: ratio				
arithmetic mean (standard deviation)	82 (± 6)	83 (± 4)	81 (± 5)	

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	baseline v Fostair v placebo
Number of subjects included in analysis	51
Analysis specification	Post-hoc
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)

Secondary: KBILD

End point title	KBILD

End point description:

measuring total score for Kings Brief questionnaire for interstitial lung disease

End point type	Secondary

End point timeframe:

measured at baseline, following 4 weeks placebo and following 4 weeks fostair

End point values	baseline	Fostair	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	17	17[12]	
Units: score				
arithmetic mean (standard deviation)	73 (± 17)	72 (± 19)	72 (± 20)	

Notes:

[12] - not parallel study crossover on 17 analysed

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	baseline v Fostair v placebo
Number of subjects included in analysis	51
Analysis specification	Post-hoc
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were reported at baseline, following 4 weeks treatment with placebo at the end of the 4 week interval (no therapy) and at the end of the 4 week treatment with fostair.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Full analysis set
Reporting group description: full analysis set	

Serious adverse events	Full analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Cerebral ischaemia	Additional description: Transient Ischaemic attack		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Full analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
Nervous system disorders			
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Neck pain			

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
General disorders and administration site conditions Fatigue alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Hyponatraemia subjects affected / exposed occurrences (all) Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Gastrointestinal disorders Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Colonoscopy alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Catarrh alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Upper respiratory tract infection alternative assessment type: Non-systematic	2 / 20 (10.00%) 4 1 / 20 (5.00%) 1		

subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
sore throat			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nasal polyps			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pharyngitis bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oral candidiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dysphonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Local reaction			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Muscle spasms	Additional description: leg cramps		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2014	1)Prohibited mediciation:- Irreversible cyclo-oxygenase inhibitors- Aspirin. To remove this class of medications from the list 2)Inclusion critera: 4. FVC of 50-80% predicted. To change this criteria to FVC of 50-110% predicted.
21 November 2014	1) Extension of certificate of analysis on the fostair/placebo inhalers 2) Supply of 20 additional kits with expiry increased to April 2015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/2925571