Clinical trial results:
A guideline approach to therapy step-down utilising Flutiform®: change and step-down (FFLU-X study)

Summary

EudraCT number	2013-005365-39
Trial protocol	GB
Global end of trial date	26 February 2016

Results information

Result version number	v1 (current)
This version publication date	26 January 2021
First version publication date	26 January 2021

Trial information

Trial identification

Sponsor protocol code	OR00213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	PCRN: 2942

Notes:

Sponsors

Sponsor organisation name	Research in Real-Life
Sponsor organisation address	5 Coles Lane, Cambridge, United Kingdom,
Public contact	Anu Kemppinen, Research in Real-Life Ltd, +44 01223967886, anu@rirl.org
Scientific contact	Anu Kemppinen, Research in Real-Life Ltd, +44 01223967886, anu@rirl.org

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	17 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2016
Global end of trial reached?	Yes
Global end of trial date	26 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study has two phases. The primary objective of each phase is as follows:

Phase 1: to test effectiveness of a recently licensed inhaler treatment, Flutiform®, against the effectiveness of a commonly used Seretide® Evohaler® inhaler in controlling asthma in real-life patients.

Phase 2: to test if asthma control can be maintained with a reduced dosage of Flutiform®

Protection of trial subjects:

Routine care

Background therapy: -

Evidence for comparator: -

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: 225
Worldwide total number of subjects	225
EEA total number of subjects	0

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)	164
From 65 to 84 years	61

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at 29 National Health Service (NHS) primary care centres across England. Recruitment period was 1 July 2014-26 February 2016.

Pre-assignment

Screening details:

A total of 259 patients with asthma were screened. Of these, 225 patients at 27 centres in the UK were randomised 2:1 into Phase 1, 151 patients to FP/FOR(1000) and 74 patients to FP/SAL(1000]) (Figure 3). A total of 34 patients were not enrolled because of screening failure.

Period 1

Period 1 title	Phase 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	FP/FOR(1000)

Arm description:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)

Arm type	Experimental
Investigational medicinal product name	Flutiform® 250
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily

Arm title	FP/SAL(1000)

Arm description:

Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily (as Seretide® 250 Evohaler®)

Arm type	Active comparator
Investigational medicinal product name	Seretide® 250 Evohaler®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily

Number of subjects in period 1	FP/FOR(1000)	FP/SAL(1000)
Started	151	74
Completed	134	73
Not completed	17	1
Consent withdrawn by subject	1	-
not recorded	2	-
Adverse event, non-fatal	7	-
Lost to follow-up	6	1
Protocol deviation	1	-

Period 2

Period 2 title	Phase 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	FP/FOR(1000)

Arm description:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)

Arm type	Active comparator
Investigational medicinal product name	Flutiform® 250
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily

Arm title	FP/FOR(500)

Arm description:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 125µg/5µg 2 puffs twice daily (as Flutiform® 125)

Arm type	Experimental
Investigational medicinal product name	FP/FOR(500)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone Propionate/Formoterol Fumarate Dihydrate 125µg/5µg 2 puffs twice daily (as Flutiform® 125)

Number of subjects in period 2[1]	FP/FOR(1000)	FP/FOR(500)
Started	58	58
Completed	54	53
Not completed	4	5
Adverse event, serious fatal	-	1
not recorded	1	-
Adverse event, non-fatal	1	-
Lost to follow-up	2	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Eighteen of the 134 patients completing Phase 1 in the FP/FOR(1000) group were not randomised into Phase 2 because they did not meet the criteria for Phase 2.

Baseline characteristics

Reporting groups	
Reporting group title	FP/FOR(1000)
Reporting group description:	
Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)	
Reporting group title	FP/SAL(1000)
Reporting group description:	
Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily (as Seretide® 250 Evohaler®)	

Reporting group values	FP/FOR(1000)	FP/SAL(1000)	Total
Number of subjects	151	74	225
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	53.0	55.1	
standard deviation	± 13.4	± 13.7	-
Gender categorical			
Units: Subjects			
Female	82	43	125
Male	69	31	100

End points

End points reporting groups

Reporting group title	FP/FOR(1000)
Reporting group description:	
Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)	
Reporting group title	FP/SAL(1000)
Reporting group description:	
Fluticasone Propionate/Salmeterol Xinafoate 250µg/25µg 2 puffs twice daily (as Seretide® 250 Evohaler®)	
Reporting group title	FP/FOR(1000)
Reporting group description:	
Fluticasone Propionate/Formoterol Fumarate Dihydrate 250µg/10µg 2 puffs twice daily (as Flutiform® 250)	
Reporting group title	FP/FOR(500)
Reporting group description:	
Fluticasone Propionate/Formoterol Fumarate Dihydrate 125µg/5µg 2 puffs twice daily (as Flutiform® 125)	

Primary: ACQ7

End point title	ACQ7
End point description:	
7-question Asthma Control Questionnaire	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	FP/FOR(1000)	FP/SAL(1000)	FP/FOR(1000)	FP/FOR(500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	72	52	52
Units: score				
arithmetic mean (standard deviation)	0.7 (± 0.8)	0.8 (± 0.8)	0.7 (± 0.8)	0.8 (± 0.8)

Statistical analyses

Statistical analysis title	Non-inferiority Phase 1
Comparison groups	FP/FOR(1000) v FP/SAL(1000)

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.09

Statistical analysis title	Non-inferiority Phase 2
Comparison groups	FP/FOR(500) v FP/FOR(1000)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.22

Secondary: Mini-AQLQ

End point title	Mini-AQLQ

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	FP/FOR(1000)	FP/SAL(1000)	FP/FOR(1000)	FP/FOR(500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	73	54	53
Units: Score				
arithmetic mean (standard error)	6.1 (± 1.1)	5.8 (± 1.1)	6.3 (± 0.9)	6.2 (± 1.1)

Statistical analyses

Statistical analysis title	Mini-AQLQ Phase 1
Comparison groups	FP/FOR(1000) v FP/SAL(1000)
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.53

Statistical analysis title	Mini-AQLQ Phase 2
Comparison groups	FP/FOR(500) v FP/FOR(1000)
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.24

Secondary: GINA	
End point title	GINA
End point description:	
Asthma control according to Global Initiative for Asthma (GINA)	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	FP/FOR(1000)	FP/SAL(1000)	FP/FOR(1000)	FP/FOR(500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124	73	54	53
Units: number of patients				
Controlled	71	28	30	26
Partially controlled	53	33	15	19
Uncontrolled	10	12	9	8

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Phase 1 (12 weeks) and Phase 2 (12 weeks)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Phase 1 FP/FOR(1000)
Reporting group description: -	
Reporting group title	Phase 1 FP/SAL(1000)
Reporting group description: -	
Reporting group title	Phase 2 FP/FOR(500)
Reporting group description: -	
Reporting group title	Phase 2 FP/FOR(1000)
Reporting group description: -	

Serious adverse events	Phase 1 FP/FOR(1000)	Phase 1 FP/SAL(1000)	Phase 2 FP/FOR(500)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)	2 / 74 (2.70%)	2 / 58 (3.45%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
Intentional self-injury			
subjects affected / exposed	0 / 151 (0.00%)	1 / 74 (1.35%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 151 (0.00%)	0 / 74 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Pneumonia bacterial			

subjects affected / exposed	0 / 151 (0.00%)	1 / 74 (1.35%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 151 (0.00%)	0 / 74 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2 FP/FOR(1000)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 58 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Intentional self-injury			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia bacterial			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 1 FP/FOR(1000)	Phase 1 FP/SAL(1000)	Phase 2 FP/FOR(500)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 151 (22.52%)	21 / 74 (28.38%)	34 / 58 (58.62%)
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	9 / 151 (5.96%)	4 / 74 (5.41%)	12 / 58 (20.69%)
occurrences (all)	9	4	13
Oropharyngeal pain			
subjects affected / exposed	6 / 151 (3.97%)	1 / 74 (1.35%)	4 / 58 (6.90%)
occurrences (all)	7	1	4
Cough			
subjects affected / exposed	7 / 151 (4.64%)	5 / 74 (6.76%)	6 / 58 (10.34%)
occurrences (all)	7	5	6
Lower respiratory tract infection			
subjects affected / exposed	5 / 151 (3.31%)	4 / 74 (5.41%)	6 / 58 (10.34%)
occurrences (all)	5	4	6
Productive cough			
subjects affected / exposed	1 / 151 (0.66%)	2 / 74 (2.70%)	3 / 58 (5.17%)
occurrences (all)	1	2	3
Asthma			
subjects affected / exposed	5 / 151 (3.31%)	4 / 74 (5.41%)	4 / 58 (6.90%)
occurrences (all)	5	4	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 151 (1.32%)	1 / 74 (1.35%)	3 / 58 (5.17%)
occurrences (all)	2	1	3
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 151 (1.99%)	2 / 74 (2.70%)	4 / 58 (6.90%)
occurrences (all)	3	2	4

Non-serious adverse events	Phase 2 FP/FOR(1000)		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	29 / 58 (50.00%)		
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	17		
Oropharyngeal pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	6		
Lower respiratory tract infection			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	7		
Productive cough			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Asthma			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2014	Substantial Amendment 1 (dated 28 January 2014) to the protocol was issued before any patient was enrolled into the study. The amendments were as follows: - The requirement for patients to have had at least 4 prescriptions of Seretide® 250 Evohaler® in the last 6 months before screening was removed; it was only required that the patient be on Seretide® 250 Evohaler® for the last 6 months before screening. The minimum number of prescriptions was initially set to at least 4 with the aim of ensuring adherence to treatment prior to study. However, this was removed given that the number of inhalers prescribed is unlikely to be a very accurate estimator of adherence. - Inclusion criteria "Step 4 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines" was removed as patients who are on Seretide® 250 Evohaler® are by definition at Step 4. - While ACQ7<1.5 was not listed in the inclusion criteria, this criterion was erroneously mentioned elsewhere in the protocol text and was removed to be consistent with the inclusion criteria listed. - In Appendix C: "Actuation not corresponding with inhalation; actuation before inhalation or too late after inhalation (more than 2 seconds)" was erroneously listed as an error when using a spacer. This has been corrected. - For randomisation to both Phase 1 and Phase 2, number of exacerbations in the 12 months prior to Phase 1 was considered; in the protocol version 1.0, it was erroneously stated that, for Phase 2 randomisation, the number of exacerbations in the 12 months before Phase 2 would be considered.
17 November 2014	Substantial Amendment 2 (dated 17 November 2014) to the protocol was issued after 23 patients had been enrolled into the study. It included both substantial and non-substantial changes to the protocol, as follows: - Substantial amendment to increase compensation to patients from £20 to £25/visit - Non-substantial change of wording from "nurse" to "healthcare professional" in protocol and other relevant study documents to reflect that both nurses and pharmacists were recruiting patients and conducting clinics for the study - A dedicated phone-line and website was set up for patients to express interest There was no impact on the patients already enrolled into the study and this Amendment did not result in any changes that would impact outcomes or analyses of data.

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/28351782