Clinical trial results:
A single (assessor) - blind, randomised, three-period, cross-over study to compare the safety of flutiform® pMDI, fluticasone pMDI and beclometasone Autohaler® in paediatric subjects aged 5 to less than 12 years with mild persistent asthma by means of knemometry.

Summary

EudraCT number	2013-004719-32
Trial protocol	DK
Global end of trial date	13 June 2014

Results information

Result version number	v1 (current)
This version publication date	09 February 2016
First version publication date	03 July 2015

Trial information

Trial identification

Sponsor protocol code	FLT2504

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02063139
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mundipharma Research Ltd.
Sponsor organisation address	Cambridge Science Park, Milton Road, Cambridge, United Kingdom, CB4 0GW
Public contact	European Medical Operations, Mundipharma Research Ltd, 0044 1223 424900, info@contact-clinical-trails.com
Scientific contact	European Medical Operations, Mundipharma Research Ltd, 0044 1223 424900, info@contact-clinical-trails.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2014
Global end of trial reached?	Yes
Global end of trial date	13 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To show non-inferiority of flutiform pMDI 50/5 µg (2 puffs bid) versus fluticasone pMDI 50 µg (2 puffs bid) based on the mean lower leg growth rates.

Protection of trial subjects:

Over the course of the study there were 3 periods of 2 weeks each (the run-in and 2 washout periods) during which subjects were not treated with inhaled corticosteroids (but were able to use salbutamol rescue medication). To minimise the risk to subjects during these periods, only children with mild asthma treated with a short acting beta agonist (SABA) alone or non-ICS controller were enrolled such that the risk of not administering inhaled corticosteroids during the run-in / washout periods was low. Regarding the ethics of conducting a growth suppressive study, the total treatment-related growth inhibition during this short-term trial would have been expected to be less than 1 millimetre. Furthermore this inhibition would cease on discontinuation of the study treatment and no long-term residual impacts on growth would be expected.

Background therapy:

Salbutamol Airomir® Autohaler® rescue medication (breath actuated inhaler) was used in the run in, wash-out and treatment periods, as required, up to four occasions per day (2 puffs on each occasion). If a subject required rescue medication on more than 4 occasions on any day they were to contact the Investigator.

Evidence for comparator:

Flixotide Evohaler was chosen as the primary comparator as it contains the same ICS component as Flutiform and represents the same pharmaceutical form (a pressurised metered dose inhaler). The benefit:risk of Flixotide in paediatric asthma is long established hence this product is an appropriate comparator against which to gauge the safety of the ICS component of Flutiform. Both products were used in conjunction with a spacer device, which is consistent with the GINA recommendation to use a pMDI in conjunction with a spacer as a first line device option in paediatric asthma.

A third treatment arm, Aerobec Autohaler (also known as QVAR Autohaler), containing the ICS Beclometasone, was included in the study for exploratory purposes to evaluate potential differences in suppressive effects between different ICS / device combinations and to serve as a positive control. The Autohaler is a breath-actuated pressurised metered dose inhaler approved for use in children aged 5 and above in Denmark and multiple other EU member states.

Actual start date of recruitment	24 February 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	Denmark: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All 48 subjects were randomised in one site in Denmark between 10 Mar 2014 and 27 Mar 2014.

Pre-assignment

Screening details:

A total of 48 subjects provided written informed consent and were screened and, as no subjects failed screening, all 48 subjects were randomised into the study.
Two subjects discontinued early from the study due to subject's choice.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The assessor undertaking lower leg measurements via knemometry was blinded to study treatment (the "assessing" investigator). A different "treating" investigator was responsible for supervising study treatment.The subject and treating investigator were open to the treatment being taken during each treatment period. The study team, including persons involved in conducting the analysis of the study, remained blinded to the treatments patients were randomised to until after study database lock.

Arms

Are arms mutually exclusive?	No
Arm title	Flutiform

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Flutiform
Investigational medicinal product code	
Other name	Fluticasone/ formoterol
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50/5 µg, 2 puffs, Q12h

Arm title	Fluticasone

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Flixotide
Investigational medicinal product code	
Other name	Fluticasone propionate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 µg, 2 puffs, Q12h

Arm title	Beclometasone

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Beclometasone
Investigational medicinal product code	
Other name	QVAR
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

50 µg, 2 puffs, Q12h

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The investigator and patient were un-blinded. The Assessor taking the measurements was blinded and therefore the single blinded description. The system does not allow us to enter this without giving the warning.

Number of subjects in period 1	Flutiform	Fluticasone	Beclometasone
Started	48	48	48
Run-in	48	48	48
Treatment Period 1	48	48	48
Wash-out Period 1	48	48	48
Treatment Period 2	48	48	48
Wash-out Period 2	48	48	48
Treatment Period 3	48	48	46
Post Study	48	48	46
Completed	48	48	46
Not completed	0	0	2
Consent withdrawn by subject	-	-	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	48	48	
Age categorical Units: Subjects			
Children (5-11)	48	48	
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	8.7		
standard deviation	± 1.65	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	38	38	

Subject analysis sets

Subject analysis set title	Randomised Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who were randomised to a treatment sequence.

Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised subjects who received at least one dose of investigational medicinal product (IMP) and had a valid baseline and at least one valid post-baseline lower leg growth rate value

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All overall Full Analysis Population subjects without major protocol deviations.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was defined as all randomised subjects who received at least one dose of study

medication (IMP).

Reporting group values	Randomised Population	Full Analysis Population	Per Protocol Population
Number of subjects	48	48	38
Age categorical			
Units: Subjects			
Children (5-11)	48	48	38
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	8.7	8.7	8.8
standard deviation	± 1.65	± 1.65	± 1.54
Gender categorical			
Units: Subjects			
Female	10	10	8
Male	38	38	30

Reporting group values	Safety Population		
Number of subjects	48		
Age categorical			
Units: Subjects			
Children (5-11)	48		
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	8.7		
standard deviation	± 1.65		
Gender categorical			
Units: Subjects			
Female	10		
Male	38		

End points

End points reporting groups

Reporting group title	Flutiform
Reporting group description: -	
Reporting group title	Fluticasone
Reporting group description: -	
Reporting group title	Beclometasone
Reporting group description: -	
Subject analysis set title	Randomised Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who were randomised to a treatment sequence.	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects who received at least one dose of investigational medicinal product (IMP) and had a valid baseline and at least one valid post-baseline lower leg growth rate value	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
All overall Full Analysis Population subjects without major protocol deviations.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population was defined as all randomised subjects who received at least one dose of study medication (IMP).	

Primary: Difference in mean lower leg growth rate (LLGR) between Flutiform and Fluticasone treatments

End point title	Difference in mean lower leg growth rate (LLGR) between Flutiform and Fluticasone treatments[1]
End point description:	
Measurement of lower leg growth (LLG) using the knemometer was taken at each visit by an assessor who was blinded to the study treatment. Knemometry measurements at visits 1 to 7 were taken at the same time (+/- 1 hour) on the same day of the week whenever possible, corresponding to the beginning and the end of each treatment or wash-out period. For each subject LLG in each period (run-in, treatment, washout) was calculated as the change in LLL during the respective period. The primary analysis was based on LLG in treatment period.	
End point type	Primary
End point timeframe:	
Each Treatment Phase was 14 days, separated by 14 days for the wash-out period.	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Each endpoint listed compares 2 out of the 3 arms in the baseline period. The 3 endpoints include reporting statistics for all 3 arms.

End point values	Flutiform	Fluticasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: mm/week				
least squares mean (confidence interval 95%)	0.417 (0.349 to 0.486)	0.423 (0.355 to 0.491)		

Statistical analyses

Statistical analysis title	Non-inferiority of Flutiform versus Fluticasone

Statistical analysis description:

The null hypothesis was: -0.2 > μFlutiform - μfluticasone

The mean lower leg growth rate during treatment (mm/week) was analysed using an Analysis of Covariance (ANCOVA) model, with fixed terms for treatment, period, treatment sequence, baseline lower leg growth rate and FEV1% predicted value at baseline and subject within sequence as a random effect.

Comparison groups	Flutiform v Fluticasone
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.095
upper limit	0.084

Notes:

[2] - A non-inferiority margin of -0.2mm/week was used, based on an estimated placebo growth rate of 0.4mm/week, the observation, that 25 to 50% reduction in short-term lower leg growth rate translates to a reduction in medium term growth rate of between 0.5 to 1.5cm/year, and considering the technical error margin of 0.1mm associated with knemometry. The intended power for the test of non-inferiority of Flutiform versus Fluticasone was set to 90%.

[3] - The null hypothesis was tested with a one-sided significance level of 0.025 (being equivalent to a two-sided test at a 0.05 level of significance).

Primary: Difference in mean lower leg growth rate (LLGR) between Flutiform and Beclometasone treatments

End point title	Difference in mean lower leg growth rate (LLGR) between Flutiform and Beclometasone treatments[4]

End point description:

Measurement of lower leg growth using the knemometer was taken at each visit by an assessor who was blinded to the study treatment. Knemometry measurements at visits 1 to 7 were taken at the same time (+/- 1 hour) on the same day of the week whenever possible, corresponding to the beginning and the end of each treatment or wash-out period. For each subject LLG in each period (run-in, treatment, washout) was calculated as the change in LLL during the respective period. The primary analysis was based on LLG in treatment period.

End point type	Primary

End point timeframe:

Each Treatment Phase was 14 days, separated by 14 days for the wash-out period.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Each endpoint listed compares 2 out of the 3 arms in the baseline period. The 3 endpoints include reporting statistics for all 3 arms.

End point values	Flutiform	Beclometasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: mm/week				
least squares mean (confidence interval 95%)	0.385 (0.29 to 0.48)	0.269 (0.174 to 0.364)		

Statistical analyses

Statistical analysis title	Superiority of Flutiform versus Beclometasone

Statistical analysis description:

The null hypothesis was that the difference in means is 0 mm/week

The mean lower leg growth rate during treatment (mm/week) was analysed using an Analysis of Covariance (ANCOVA) model, with fixed terms for treatment, period, treatment sequence, baseline growth rate and FEV1% predicted value at baseline and subject within sequence as a random effect.

Comparison groups	Flutiform v Beclometasone
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.057 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.235

Notes:

[5] - A difference of 0 mm/week was used.

[6] - 2-sided p-value of treatment comparison based on the null hypothesis that the difference in means is 0 mm/week.

Primary: Difference in mean lower leg growth rate (LLGR) between Fluticasone and Beclometasone treatments

End point title	Difference in mean lower leg growth rate (LLGR) between Fluticasone and Beclometasone treatments[7]

End point description:

Measurement of lower leg growth using the knemometer was taken at each visit by an assessor who was blinded to the study treatment. Knemometry measurements at visits 1 to 7 were taken at the same time (+/- 1 hour) on the same day of the week whenever possible, corresponding to the beginning and the end of each treatment or wash-out period. For each subject LLG in each period (run-in, treatment, washout) was calculated as the change in LLL during the respective period. The primary analysis was based on LLG in treatment period.

End point type	Primary

End point timeframe:

Each Treatment Phase was 14 days, separated by 14 days for the wash-out period.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Each endpoint listed compares 2 out of the 3 arms in the baseline period. The 3 endpoints include reporting statistics for all 3 arms.

End point values	Fluticasone	Beclometasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: mm/week				
least squares mean (confidence interval 95%)	0.399 (0.337 to 0.46)	0.235 (0.174 to 0.296)		

Statistical analyses

Statistical analysis title	Superiorty of Fluticasone versus Beclometasone
Statistical analysis description:	
The null hypothesis was that the difference in means is 0 mm/week.	
Comparison groups	Beclometasone v Fluticasone
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.249

Notes:

[8] - The mean lower leg growth rate during treatment (mm/week) was analysed using an Analysis of Covariance (ANCOVA) model, with fixed terms for treatment, period, treatment sequence, baseline lower leg growth rate and FEV1% predicted value at baseline and subject within sequence as a random effect.
[9] - 2-sided p-value of treatment comparison based on the null hypothesis that the difference in means is 0 mm/week.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the point at which the Informed Consent was signed until 7 days after the subject left the study. This included new AEs that were reported in the 7 days following the subject's completion/discontinuation visit.

Adverse event reporting additional description:

Any AE that was still ongoing 7 days after the completion/discontinuation visit had an outcome of 'ongoing' in the CRF; SAEs were followed until the event resolved or the event or sequelae stabilized. A treatment emergent AE was defined as any AE with an onset date on or after the first dose of IMP, or worsened after the first dose of IMP.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Flutiform
Reporting group description: -	
Reporting group title	Fluticasone
Reporting group description: -	
Reporting group title	Beclometasone

Reporting group description: -

Serious adverse events	Flutiform	Fluticasone	Beclometasone
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 46 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Flutiform	Fluticasone	Beclometasone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)	3 / 48 (6.25%)	3 / 46 (6.52%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 48 (4.17%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Eye disorders			

Conjunctivitis allergic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 48 (2.08%)	2 / 48 (4.17%)	1 / 46 (2.17%)
occurrences (all)	1	2	1
Psychiatric disorders			
Anger			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Eye infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported