Clinical trial results:
A double-blind, double dummy, randomised, parallel group, multicentre study to compare the efficacy and safety of Flutiform pMDI with fluticasone pMDI and with Seretide pMDI in paediatric subjects aged 5 to less than 12 years with moderate to severe persistent reversible asthma.

Summary

EudraCT number	2010-024635-16
Trial protocol	HU CZ PL BG
Global end of trial date	04 September 2013

Results information

Result version number	v1 (current)
This version publication date	13 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	FLT3506

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01511367
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 Limited, +44 1223424900, info@contact-clinical-trials.com
Scientific contact	European Medical Operations, Mundipharma Research Limited, +44 1223424900, info@contact-clinical-trials.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000127-PIP01-07
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	04 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2013
Global end of trial reached?	Yes
Global end of trial date	04 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to show superiority in the efficacy of Flutiform pMDI 50/5µg (2 puffs bid) versus fluticasone pMDI 50 µg (2 puffs bid).

Protection of trial subjects:

All subjects and their guardians/legally authorised representatives were provided with oral and written information describing the nature and duration of the study, its purpose, the procedures to be performed, the potential risks and benefits involved, and any potential discomfort. Each subject was given a copy of the PIS and ICF. The subject's guardian /legally authorised representative was asked to sign an informed consent form and, according to local country requirements and where appropriate, the subject was asked to sign/mark (e,g. drawing if subject was very young) an informed assent form (IAF) prior to any study-specific procedures being performed. No subject could enter the study before his/her guardian's/legally authorised representative's informed consent had been obtained.

Background therapy:

Salbutamol 100 µg was used as rescue medication in the run-in and treatment period.

Evidence for comparator:

Seretide was chosen as a comparator product because it is a marketed asthma medication consisting of an ICS and a LABA within a pMDI. The choice of Seretide (in some countries known as Viani® or Advair®) also maintains consistency across the treatment for the steroid part of the combinations (fluticasone). Seretide is a market leader within the field of asthma and is licensed for use in children aged 4 years or older.

Actual start date of recruitment	26 March 2012
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	Bulgaria: 90
Country: Number of subjects enrolled	Poland: 187
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Hungary: 107
Country: Number of subjects enrolled	India: 10
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Ukraine: 29
Worldwide total number of subjects	512
EEA total number of subjects	401

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)	512
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: -

Pre-assignment

Screening details:

A total of 713 subjects provided written informed consent and were screened; 512 subjects were randomised and 509 subjects were treated. 150 subjects failed screening; 136 subjects due to failing the inclusion/exclusion criteria, 11 subjects chose not to continue, 2 subjects due to adverse event, and 1 subject due to administrative reasons.

Period 1

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

Blinding implementation details:

The subject and all personnel involved with the study, excluding those involved in processing and regulatory reporting of SUSARs, were blinded to the medication codes. The randomisation schedule was filed securely by the interactive response technology (IRT) provider in a manner such that blinding was properly maintained throughout the study. To maintain the blinded nature of this study, each subject received 2 inhalers.

Arms

Are arms mutually exclusive?	Yes
Arm title	Flutiform

Arm description:

Flutiform

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

Dosage and administration details:

50/5µg, 2 puffs, Q12h

Arm title	Fluticasone

Arm description:

Fluticasone

Arm type	Active comparator
Investigational medicinal product name	Fluticasone
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	Seretide

Arm description:

Seretide

Arm type	Active comparator

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

Dosage and administration details:

50/25 µg, 2 puffs, Q12h

Number of subjects in period 1	Flutiform	Fluticasone	Seretide
Started	169	173	170
Run-in	169	173	170
Treatment period	169	173	170
Completed	161	161	159
Not completed	8	12	11
Consent withdrawn by subject	1	1	-
Administrative	4	7	5
Adverse event, non-fatal	-	1	-
Lack of efficacy	3	3	6

Baseline characteristics

Reporting groups	
Reporting group title	Flutiform
Reporting group description: Flutiform	
Reporting group title	Fluticasone
Reporting group description: Fluticasone	
Reporting group title	Seretide
Reporting group description: Seretide	

Reporting group values	Flutiform	Fluticasone	Seretide
Number of subjects	169	173	170
Age categorical Units: Subjects			
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
Children (5-11 years)	169	173	170
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
Gender categorical Units: Subjects			
Female	58	55	56
Male	111	118	114

Reporting group values	Total		
Number of subjects	512		
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		
Children (5-11 years)	512		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	169		
Male	343		

Subject analysis sets

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

Subject analysis set description:

The safety population (SP) was defined as all randomised subjects who received at least one dose of study medication (IMP). Subjects were analysed according to actual treatment received.

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

Subject analysis set description:

The full analysis population (FAP) was defined as all randomised subjects who received at least one dose of study medication (IMP) and had at least one valid efficacy (FEV1) assessment. Subjects will be analysed according to their randomised treatment.

Reporting group values	Safety Population	Full Analysis Population	
Number of subjects	509	506	
Age categorical 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	
Children (5-11 years)	509	506	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	168	168	
Male	341	338	

End points

End points reporting groups

Reporting group title	Flutiform
Reporting group description: Flutiform	
Reporting group title	Fluticasone
Reporting group description: Fluticasone	
Reporting group title	Seretide
Reporting group description: Seretide	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population (SP) was defined as all randomised subjects who received at least one dose of study medication (IMP). Subjects were analysed according to actual treatment received.	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis population (FAP) was defined as all randomised subjects who received at least one dose of study medication (IMP) and had at least one valid efficacy (FEV1) assessment. Subjects will be analysed according to their randomised treatment.	

Primary: Change from pre-dose FEV1 at baseline to the 2-hour post-dose FEV1 over the 12 week treatment period

End point title	Change from pre-dose FEV1 at baseline to the 2-hour post-dose FEV1 over the 12 week treatment period
End point description: The primary endpoint, which was tested in a hierarchical (gate keeping) manner for the two study comparisons (Flutiform to Fluticasone, then Flutiform to Seretide), was the change from pre-dose Forced Expiratory Volume in 1 second (FEV1) at baseline to 2 hours post-dose FEV1 over the 12 week treatment period.	
End point type	Primary
End point timeframe: From baseline to the 2-hour post-dose values over the 12 weeks.	

End point values	Flutiform	Fluticasone	Seretide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	165	165	
Units: Litres				
least squares mean (confidence interval 95%)	0.22 (0.18 to 0.26)	0.15 (0.11 to 0.19)	0.22 (0.18 to 0.26)	

Statistical analyses

Statistical analysis title	Superiority of Flutiform versus Fluticasone

Statistical analysis description:

Null hypothesis (H0): μ Flutiform = μ Fluticasone
Alternative (H1): μ Flutiform ≠ μ Fluticasone
The change from pre-dose FEV1 values at baseline to the 2-hour post dose FEV1 values at each post baseline visit were analysed using a repeated measures Analysis of Covariance (ANCOVA) with fixed terms for treatment, age group, pre-dose FEV1 at baseline, visit and treatment by visit interaction, and centre as a random effect.

Comparison groups	Flutiform v Fluticasone
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	ANCOVA

Notes:

[1] - Superiority was demonstrated if the primary comparison of Flutiform versus Fluticasone was significant at the 0.05 alpha level.
[2] - Based on the null hypothesis that there is no difference in treatment means.

Statistical analysis title	Non-inferiority of Flutiform versus Seretide

Statistical analysis description:

Null hypothesis (H0): μ Flutiform - μ Seretide < - 0.1
Alternative (H1): μ Flutiform - μ Seretide ≥ - 0.1
The change from pre-dose FEV1 values was analysed using a repeated measures ANCOVA with fixed terms for treatment, age group, pre-dose FEV1 at baseline, visit and treatment by visit interaction and centre as a random effect. The statistical model
was used to calculate the overall treatment difference and 95% CI.

Comparison groups	Flutiform v Seretide
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	ANCOVA

Notes:

[3] - Non-inferiority was concluded if the lower limit of the 95% (confidence interval) CI was greater than or equal to -0.1L and the p-value for the non-inferiority comparison was based on a treatment difference of -0.1L.
[4] - P-value of the pairwise treatment comparisons (based on the null hypothesis that the difference in treatment means is -0.1L).

Secondary: FEV1 AUC0-4h at Week 12

End point title	FEV1 AUC0-4h at Week 12

End point description:

Normalised four hour FEV1 area under the curve values at Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Flutiform	Fluticasone	Seretide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	147	152	
Units: Litres/hour				
least squares mean (confidence interval 95%)	1.8 (1.75 to 1.84)	1.71 (1.66 to 1.76)	1.79 (1.74 to 1.83)	

Statistical analyses

Statistical analysis title	Superiority of Flutiform versus Fluticasone

Statistical analysis description:

Null hypothesis (H0): μ Flutiform = μ Fluticasone
Alternative (H1): μ Flutiform ≠ μ Fluticasone
The normalised 4-hour FEV1 AUC0-4h values at Week 12 were analysed using an ANCOVA with fixed terms for treatment, age group, pre-dose FEV1 at baseline, and centre as a random effect.

Comparison groups	Flutiform v Fluticasone
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	ANCOVA

Notes:

[5] - Superiority was demonstrated if the primary comparison of Flutiform versus Fluticasone was significant at the 0.05 alpha level.
[6] - P-value of the pairwise treatment comparisons (based on the null hypothesis that there is no difference in treatment means).

Statistical analysis title	Non-inferiority of Flutiform versus Seretide

Statistical analysis description:

Null hypothesis (H0): μ Flutiform - μ Seretide < - 0.1
Alternative (H1): μ Flutiform - μ Seretide ≥ - 0.1
The change from pre-dose FEV1 values from baseline to each post baseline visit over the 12 weeks was analysed using a repeated measures ANCOVA with fixed terms for treatment, age group, pre-dose FEV1 at baseline, visit and treatment by visit interaction and centre as a random effect.

Comparison groups	Flutiform v Seretide
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001 [8]
Method	ANCOVA

Notes:

[7] - Non-inferiority was concluded if the lower limit of the 95% (confidence interval) CI was greater than or equal to -0.1L. The statistical model was used to calculate the overall treatment difference and 95% CI.
[8] - P-value of the pairwise treatment comparisons (based on the null hypothesis that the difference in treatment means is -0.1L).

Secondary: Change from pre-dose FEV1 at baseline over the 12 week treatment period

End point title	Change from pre-dose FEV1 at baseline over the 12 week treatment period

End point description:

Change from pre-dose Forced Expiratory Volume in 1 second (FEV1) from baseline over the 12 week treatment period.

End point type	Secondary

End point timeframe:

From baseline to each post baseline visit over 12 weeks.

End point values	Flutiform	Fluticasone	Seretide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	171	165	
Units: Litres				
least squares mean (confidence interval 95%)	0.13 (0.09 to 0.17)	0.1 (0.06 to 0.14)	0.16 (0.12 to 0.2)	

Statistical analyses

Statistical analysis title	Superiority of Flutiform versus Fluticasone

Statistical analysis description:

Null hypothesis (H0): μ Flutiform = μ Fluticasone
Alternative (H1): μ Flutiform ≠ μ Fluticasone
The change from pre-dose FEV1 values from baseline to each post baseline visit over 12 weeks was analysed using a repeated measures ANCOVA with fixed terms for treatment, age group, pre-dose FEV1 at baseline, visit and treatment by visit interaction, and centre as a random effect. The statistical model was used to calculate the overall treatment difference and 95% CI.

Comparison groups	Fluticasone v Flutiform
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.091 [10]
Method	ANCOVA

Notes:

[9] - Superiority was demonstrated if the primary comparison of Flutiform versus Fluticasone was significant at the 0.05 alpha level.
[10] - P-value of the pairwise treatment comparisons (based on the null hypothesis that there is no difference in treatment means).

Statistical analysis title	Non-inferiority of Flutiform versus Seretide

Statistical analysis description:

Null hypothesis (H0): μ Flutiform - μ Seretide < - 0.1
Alternative (H1): μ Flutiform - μ Seretide ≥ - 0.1
The change from pre-dose FEV1 values from baseline to each post baseline visit over 12 weeks was analysed using a repeated measures ANCOVA with fixed terms for treatment, age group, pre-dose FEV1 at baseline, visit and treatment by visit interaction and centre as a random effect.

Comparison groups	Flutiform v Fluticasone v Seretide
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001 [12]
Method	ANCOVA

Notes:

[11] - Non-inferiority was concluded if the lower limit of the 95% (confidence interval) CI was greater than or equal to -0.1L and the p-value for the non-inferiority comparison was based on a treatment difference of -0.1L.

[12] - P-value of the pairwise treatment comparisons (based on the null hypothesis that the difference in treatment means is -0.1L).

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 14 days after the subject left the study. This included new AEs that were reported in the 14 days following the subject's completion/discontinuation visit.

Adverse event reporting additional description:

Only treatment emergent AEs were summarised. A treatment emergent AE was defined as any AE with an onset date on or after the first dose of study medication if the AE was absent before the first dose of study medication, or worsened after the first dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Flutiform

Reporting group description:

Flutiform

Reporting group title	Fluticasone

Reporting group description:

Fluticasone

Reporting group title	Seretide

Reporting group description:

Seretide

Serious adverse events	Flutiform	Fluticasone	Seretide
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 168 (0.60%)	1 / 172 (0.58%)	0 / 169 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 168 (0.00%)	1 / 172 (0.58%)	0 / 169 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 172 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Flutiform	Fluticasone	Seretide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 168 (22.62%)	52 / 172 (30.23%)	35 / 169 (20.71%)
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 168 (1.19%)	4 / 172 (2.33%)	2 / 169 (1.18%)
occurrences (all)	3	4	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 168 (1.79%)	2 / 172 (1.16%)	4 / 169 (2.37%)
occurrences (all)	3	2	5
Nasopharyngitis			
subjects affected / exposed	4 / 168 (2.38%)	15 / 172 (8.72%)	13 / 169 (7.69%)
occurrences (all)	4	20	14
Pharyngitis			
subjects affected / exposed	4 / 168 (2.38%)	7 / 172 (4.07%)	4 / 169 (2.37%)
occurrences (all)	6	8	4
Rhinitis			
subjects affected / exposed	8 / 168 (4.76%)	4 / 172 (2.33%)	4 / 169 (2.37%)
occurrences (all)	11	4	6
Viral rhinitis			
subjects affected / exposed	1 / 168 (0.60%)	2 / 172 (1.16%)	4 / 169 (2.37%)
occurrences (all)	1	2	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2013	Protocol Amendment No. 3 was a substantial amendment which revised the study objectives and amended the statistical analysis accordingly following Scientific advice from the MHRA. The approved indication for Flutiform in adults and adolescents includes a "switch" to Flutiform in patients already adequately controlled on a combination of an inhaled corticosteroid and a long-acting β2 agonist. In the light of this indication, at a scientific advice meeting on the 27th February 2013, the MHRA advised the sponsor to revise the paediatric study objectives and to designate non-inferiority versus Seretide as a key secondary objective. Although the Paediatric Development Committee (PDCO) had already endorsed the design and comparisons in the original study, in order to accommodate the MHRA's recommendation the sponsor altered the designation of comparators accordingly and amended the original sequence of statistical tests in order to control the Type 1 error rate. Furthermore given the confirmatory nature of the comparison versus Seretide in the amended protocol the primary timepoint for this comparison was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported