



Clinical trial results:

A Randomised, Multi-Centre, Double-Blind, Double-Dummy, Two Way Cross-Over, Twelve Weeks Non-inferiority Study to Evaluate the Efficacy, Safety, and Tolerability of Combination Dry Powder of Fluticasone Propionate and Salmeterol 250/50 mcg Twice Daily Delivered through a Capsule-Based Inhaler and a Multi-Dose Inhaler in Adults and Adolescents with Asthma

Summary

EudraCT number	2015-004893-14
Trial protocol	Outside EU/EEA
Global end of trial date	28 January 2015

Results information

Result version number	v1 (current)
This version publication date	25 January 2017
First version publication date	25 January 2017

Trial information

Trial identification

Sponsor protocol code	115645
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	16 March 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2013
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	Russian Federation: 75
Country: Number of subjects enrolled	Ukraine: 49
Worldwide total number of subjects	124
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)	1
Adolescents (12-17 years)	4
Adults (18-64 years)	96
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 124 participants (par) were enrolled into the study, 33 participants were screen failures and 7 participants were run-in failures. A total of 84 participants were randomised and 82 participants were included in Intend to treat (ITT) population.

Period 1

Period 1 title	Treatment Period 1 (12 weeks)
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	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI

Arm description:

Participants self administered one inhalation of matching Placebo (PI) via a multi-dose dry powder inhaler (MD DPI) and one inhalation of single capsule containing Fluticasone salmeterol combination (FSC) (250/50 microgram [mcg]) via a capsule-based unit dose (CB) DPI in the morning and evening in the Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of FSC (250/50 mcg) via the multi-dose DPI and one inhalation of matching Placebo via the capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Arm type	Experimental
Investigational medicinal product name	Fluticasone Propionate/Salmeterol Combination (FSC) (250/50 µg) – Capsule-Based (CB) unit dose DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of FSC (250/50 µg) twice daily (BID) from a CB DPI, for 12 weeks in one treatment period.

Investigational medicinal product name	Placebo to match FSC CB DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo twice daily (BID) from a CB DPI, for 12 weeks in one treatment period.

Arm title	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
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Arm description:

Participants self administered one inhalation of FSC (250/50 mcg) via a multi-dose DPI and one inhalation of Placebo via a capsule-based unit dose DPI in the morning and evening in Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of matching Placebo via a multi-dose DPI and one inhalation of FSC (250/50 mcg) via a capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Arm type	Experimental
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Investigational medicinal product name	Fluticasone Propionate/Salmeterol Combination (FSC) (250/50 µg) – Multi-Dose (MD) DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of FSC (250/50 µg) twice daily (BID) from a MD DPI, for 12 weeks in one treatment period.

Investigational medicinal product name	Placebo to match FSC MD DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo twice daily (BID) from a MD DPI, for 12 weeks in one treatment period.

Number of subjects in period 1^[1]	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Started	40	42
Completed	38	42
Not completed	2	0
Consent withdrawn by subject	1	-
Participants reached stopping criteria	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Total 124 participants (par) were enrolled into the study, 33 participants were screen failures and 7 participants were run-in failures. A total of 84 participants were randomized and 82 participants were included in Intend to treat (ITT) population. The 2 participants were randomly assigned to treatment but were withdrawn prior to receiving study drug due to protocol deviations and were therefore not included in the ITT Population.

Period 2

Period 2 title	Washout Period 1 (3 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI

Arm description:

Participants self administered one inhalation of matching Placebo (PI) via a multi-dose dry powder inhaler (MD DPI) and one inhalation of single capsule containing Fluticasone salmeterol combination (FSC) (250/50 microgram [mcg]) via a capsule-based unit dose (CB) DPI in the morning and evening in the Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of FSC (250/50 mcg) via the multi-dose DPI and one inhalation of of matching Placebo via the capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Arm description: Participants self administered one inhalation of FSC (250/50 mcg) via a multi-dose DPI and one inhalation of Placebo via a capsule-based unit dose DPI in the morning and evening in Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of matching Placebo via a multi-dose DPI and one inhalation of FSC (250/50 mcg) via a capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Started	38	42
Completed	38	42

Period 3

Period 3 title	Treatment Period 2 (12 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI

Arm description:

Participants self administered one inhalation of matching Placebo (PI) via a multi-dose dry powder inhaler (MD DPI) and one inhalation of single capsule containing Fluticasone salmeterol combination (FSC) (250/50 microgram [mcg]) via a capsule-based unit dose (CB) DPI in the morning and evening in the Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of FSC (250/50 mcg) via the multi-dose DPI and one inhalation of of matching Placebo via the capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Arm type	Experimental
Investigational medicinal product name	Placebo to match FSC CB DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo twice daily (BID) from a CB DPI, for 12 weeks in one treatment period.

Investigational medicinal product name	Fluticasone Propionate/Salmeterol Combination (FSC) (250/50 µg) – Capsule-Based (CB) unit dose DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of FSC (250/50 µg) twice daily (BID) from a CB DPI, for 12 weeks in one treatment period.

Arm title	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
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Arm description:

Participants self administered one inhalation of FSC (250/50 mcg) via a multi-dose DPI and one inhalation of Placebo via a capsule-based unit dose DPI in the morning and evening in Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of matching Placebo via a multi-dose DPI and one inhalation of FSC (250/50 mcg) via a capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Arm type	Experimental
Investigational medicinal product name	Fluticasone Propionate/Salmeterol Combination (FSC) (250/50 µg) – Multi-Dose (MD) DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of FSC (250/50 µg) twice daily (BID) from a MD DPI, for 12 weeks in one treatment period.

Investigational medicinal product name	Placebo to match FSC MD DPI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of placebo twice daily (BID) from a MD DPI, for 12 weeks in one treatment period.

Number of subjects in period 3	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Started	38	42
Completed	38	40
Not completed	0	2
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period 1 (12 weeks)
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Reporting group description:

All participants received one of the following 2 treatments in each of the two 12-week treatment periods separated by a 3-week washout period. One actuations of FSC (250/50 mcg) self administered twice daily (BID) (morning and evening) via multi-dose DPI plus one actuation of Placebo self administered BID (morning and evening) via capsule-based unit dose DPI or one actuation of Placebo self administered BID (morning and evening) via multi-dose DPI plus one actuation of FSC (250/50 mcg) self administered BID (morning and evening) via capsule-based unit dose DPI. Salbutamol/albuterol was provided to use as rescue medication.

Reporting group values	Treatment Period 1 (12 weeks)	Total	
Number of subjects	82	82	
Age categorical			
Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	52.5		
standard deviation	± 14.93	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	46	46	
Male	36	36	
Race/Ethnicity, Customized			
Units: Subjects			
White - White/Caucasian/European Heritage	82	82	

End points

End points reporting groups

Reporting group title	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI
Reporting group description: Participants self administered one inhalation of matching Placebo (PI) via a multi-dose dry powder inhaler (MD DPI) and one inhalation of single capsule containing Fluticasone salmeterol combination (FSC) (250/50 microgram [mcg]) via a capsule-based unit dose (CB) DPI in the morning and evening in the Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of FSC (250/50 mcg) via the multi-dose DPI and one inhalation of matching Placebo via the capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	
Reporting group title	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Reporting group description: Participants self administered one inhalation of FSC (250/50 mcg) via a multi-dose DPI and one inhalation of Placebo via a capsule-based unit dose DPI in the morning and evening in Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of matching Placebo via a multi-dose DPI and one inhalation of FSC (250/50 mcg) via a capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	
Reporting group title	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI
Reporting group description: Participants self administered one inhalation of matching Placebo (PI) via a multi-dose dry powder inhaler (MD DPI) and one inhalation of single capsule containing Fluticasone salmeterol combination (FSC) (250/50 microgram [mcg]) via a capsule-based unit dose (CB) DPI in the morning and evening in the Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of FSC (250/50 mcg) via the multi-dose DPI and one inhalation of of matching Placebo via the capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	
Reporting group title	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Reporting group description: Participants self administered one inhalation of FSC (250/50 mcg) via a multi-dose DPI and one inhalation of Placebo via a capsule-based unit dose DPI in the morning and evening in Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of matching Placebo via a multi-dose DPI and one inhalation of FSC (250/50 mcg) via a capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	
Reporting group title	Sequence 1: PI MD-DPI/FSC CB-DPI then FSC MD-DPI/PI CB-DPI
Reporting group description: Participants self administered one inhalation of matching Placebo (PI) via a multi-dose dry powder inhaler (MD DPI) and one inhalation of single capsule containing Fluticasone salmeterol combination (FSC) (250/50 microgram [mcg]) via a capsule-based unit dose (CB) DPI in the morning and evening in the Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of FSC (250/50 mcg) via the multi-dose DPI and one inhalation of of matching Placebo via the capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	
Reporting group title	Sequence 2: FSC MD-DPI/PI CB-DPI then PI MD-DPI/FSC CB-DPI
Reporting group description: Participants self administered one inhalation of FSC (250/50 mcg) via a multi-dose DPI and one inhalation of Placebo via a capsule-based unit dose DPI in the morning and evening in Treatment Period 1 for 12 weeks. After washout period of 3 weeks participants self administered one inhalation of matching Placebo via a multi-dose DPI and one inhalation of FSC (250/50 mcg) via a capsule-based unit dose DPI in the morning and evening in Treatment Period 2 for 12 weeks. Salbutamol/albuterol was provided to use as rescue medication.	

Subject analysis set title	FSC Capsule-Based Unit Dose DPI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received one actuation of Placebo self administered BID (morning and evening) via multi-dose DPI plus one actuation of FSC (250/50 mcg) self administered BID (morning and evening) via capsule-based unit dose DPI in either of two treatment periods for 12 weeks. Treatment periods were separated by washout period of 3 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Subject analysis set title	FSC Multi-Dose DPI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received one actuations of FSC (250/50 mcg) self administered BID (morning and evening) via multi-dose DPI plus one actuation of Placebo self administered BID (morning and evening) via capsule-based unit dose DPI in either of two treatment periods for 12 weeks. Treatment periods were separated by washout period of 3 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Primary: Change from Baseline in trough morning forced expiratory volume in 1 second (FEV1) at Day 85

End point title	Change from Baseline in trough morning forced expiratory volume in 1 second (FEV1) at Day 85
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End point description:

Pulmonary function was measured by FEV1, defined(Def) as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 is Def as morning prebronchodilator and predose (12 hours after the last evening dose Day 84). Trough FEV1 was measured electronically by spirometer in the morning, before using the bronchodilator and predose, at Week 12 (Day 85) of each Treatment (Trt) Period (Prd). Baseline (BL) was Def as value obtained predose (0 minutes) on day 1 in each Trt Prd. Change from baseline (CFBL) within each Prd was calculated as trough FEV1 at Day 85 minus Prd specific BL value. The CFBL in trough FEV1 was analysed using Mixed Model for Repeated Measures analysis, having fixed effect Par level BL, Adjusted prd-specific BL, Trt group, Prd, Visit, Visit by Trt, Visit by Par level BL, Visit by Adjusted prd-specific BL, with Par as a random effect. ITT population: All par randomly assigned to Trt who received at least 1 dose of randomised study Trt in Trt Prd.

End point type	Primary
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End point timeframe:

Baseline and Day 85.

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78 ^[1]	80 ^[2]		
Units: Liter				
least squares mean (standard error)	0.231 (± 0.0339)	0.203 (± 0.0338)		

Notes:

[1] - ITT Population. Only those par available at the specified time points were analyzed.

[2] - ITT Population. Only those par available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Capsule-Based Unit Dose DPI v FSC Multi-Dose DPI

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Method	Repeated Measures Mixed Models
Parameter estimate	Mean difference (net)
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.08

Notes:

[3] - Non- inferiority was demonstrated if lower limit of the CI (0.025 one sided significance level) for the difference of the mean change from Baseline in trough FEV1 of FSC administered BID by capsule-based unit dose DPI versus FSC administered BID by multi-dose DPI is greater than -125 milliliter (mL).

Secondary: FEV1 area under the curve from 0 to 12 hours (AUC [0-12]) on Day 1 of each Treatment Period

End point title	FEV1 area under the curve from 0 to 12 hours (AUC [0-12]) on Day 1 of each Treatment Period
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End point description:

The AUC was analysed using a mixed effects analysis of covariance (ANCOVA) with participant-level baseline (day 1 trough FEV1), adjusted period-specific baseline (day 1 trough FEV1), treatment group and period as fixed effects and participant as a random effect.

End point type	Secondary
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End point timeframe:

Day 1 of each Treatment Period

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80 ^[4]	80 ^[5]		
Units: Liter*hours				
least squares mean (standard error)	27.642 (± 0.3583)	27.995 (± 0.3583)		

Notes:

[4] - ITT Population. Only those par available at the specified time points were analyzed.

[5] - ITT Population. Only those par available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Multi-Dose DPI v FSC Capsule-Based Unit Dose DPI
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.352

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.039
upper limit	0.334

Secondary: FEV1 AUC (0-12) at Day 85 of each Treatment Period

End point title	FEV1 AUC (0-12) at Day 85 of each Treatment Period
End point description: The AUC was analysed using a mixed effects analysis of covariance (ANCOVA) with participant-level baseline (day 1 trough FEV1), adjusted period-specific baseline (day 1 trough FEV1), treatment group and period as fixed effects and participant as a random effect.	
End point type	Secondary
End point timeframe: Day 85 of each Treatment Period	

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	77 ^[6]	79 ^[7]		
Units: Liter*hours				
least squares mean (standard error)	28.317 (± 0.4307)	28.039 (± 0.4285)		

Notes:

[6] - ITT Population. Only those par available at the specified time points were analyzed.

[7] - ITT Population. Only those par available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Multi-Dose DPI v FSC Capsule-Based Unit Dose DPI
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.278
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.372
upper limit	0.927

Secondary: Change from Baseline in Morning Trough FEV1 at Day 28 and Day 56

End point title	Change from Baseline in Morning Trough FEV1 at Day 28 and Day 56
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End point description:

Pulmonary function was measured by FEV1 (measure of lung function), defined as maximal amount of air that can be forcefully exhaled in 1 second. Trough FEV1 measurements were taken electronically by spirometry at predose (BL), on Days 28 and 56 of each Trt Prd. BL was def as value obtained predose (0 minutes) on Day 1 of each Trt Prd. CFBL within each prd was calculated as trough FEV1 at Day 28 and 56 minus the prd specific BL value. The CFBL in trough FEV1 at Day 28 and Day 56 was analysed via the primary analysis model. Least Squares mean values for the CFBL in trough FEV1 at Day 28 and Day 56 were obtained from the primary analysis model (for each Trt and for the Trt difference), and displayed alongside corresponding 95% confidence intervals. Only those par available at the specified time points were analyzed (represented by n=X, X in the category titles). Par at each time point may have been different therefore a total of 82 par analyzed represents the overall ITT population.

End point type	Secondary
End point timeframe:	
Baseline, Day 28, and Day 56	

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82 ^[8]	82 ^[9]		
Units: Liter				
least squares mean (standard error)				
Day 28, n=81, 80	0.245 (± 0.0402)	0.238 (± 0.0405)		
Day 56, n=78, 80	0.224 (± 0.0378)	0.202 (± 0.0377)		

Notes:

[8] - ITT Population.

[9] - ITT Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Capsule-Based Unit Dose DPI v FSC Multi-Dose DPI
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.088

Statistical analysis title	Statistical analysis 2
Comparison groups	FSC Capsule-Based Unit Dose DPI v FSC Multi-Dose DPI

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.092

Secondary: Change from Baseline (BL) in morning Peak Expiratory Flow Rate (PEFR) over 12 Weeks (from paper Diary Card) for each Treatment Period(TP)

End point title	Change from Baseline (BL) in morning Peak Expiratory Flow Rate (PEFR) over 12 Weeks (from paper Diary Card) for each Treatment Period(TP)
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End point description:

The PEFR is a participant's(par) maximum speed of expiration, as measured with a peak flow meter(PFM). All par were issued a PFM and instructed to perform the activity in triplicate in the morning prior to taking the bronchodilator. The best among the 3 readings was selected. Efficacy measurement was recorded by the par in the paper Diary Card for morning PEFR. The total PEFR over the 12 week TP was divided by the number of days with non-missing PEFR data to obtain an average for each par. Change from BL in average morning PEFR is the difference over 12 weeks for each TP compared to BL. BL is the average of the last 4 available recorded values during the last 7 days of the Screening Period (for TP 1) and of the Washout Period (for TP 2). The change from BL in the PEFR averaged over the 12-week TP was analysed using a mixed effects ANCOVA model with participant level BL PEFR, adjusted period-specific BL PEFR, treatment group, and period as fixed effects, and par as a random effect.

End point type	Secondary
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End point timeframe:

Baseline and up to Day 85 of each Treatment Period

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81 ^[10]	80 ^[11]		
Units: Liters per minute				
least squares mean (standard error)	23.02 (± 3.325)	18.67 (± 3.338)		

Notes:

[10] - ITT population, Only those participants available at the specified time points were analyzed.

[11] - ITT population, Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Capsule-Based Unit Dose DPI v FSC Multi-Dose DPI

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	4.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	10.05

Secondary: Change from Baseline (BL) in Rescue Medication Use over 12 Weeks (from paper Diary Card) for each Treatment Period (TP)

End point title	Change from Baseline (BL) in Rescue Medication Use over 12 Weeks (from paper Diary Card) for each Treatment Period (TP)
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End point description:

Rescue medication usage for each 24-hour period is defined as the total numbers of puffs of Salbutamol/Albuterol within 24 hours (i.e. number taken during the day and number taken during the night). The total usage over the 12 week TP was divided by the number of days with nonmissing rescue medication data to get an average usage per participant. BL is the average of the last 4 available recorded values during the last 7 days of the Screening Period (for TP 1) and of the Washout Period (for TP 2). Change from BL in average usage of rescue medication was the difference over 12 weeks for each TP compared to BL. The change from BL in the percentage of rescue medication use averaged over the 12-week TP was analysed using mixed effects ANCOVA model, with par level BL rescue medication use, adjusted period-specific BL rescue medication use, treatment group and period as fixed effects and par as a random effect.

End point type	Secondary
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End point timeframe:

Baseline and up to Day 85 of each Treatment Period

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81 ^[12]	80 ^[13]		
Units: Puffs per day				
least squares mean (standard error)	-0.41 (± 0.086)	-0.36 (± 0.086)		

Notes:

[12] - ITT population, Only those participants available at the specified time points were analyzed.

[13] - ITT population, Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Multi-Dose DPI v FSC Capsule-Based Unit Dose DPI

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.09

Secondary: Change from Baseline in Day-time(AM) and Night-time (PM) Asthma Symptoms(Sy) from paper Diary Card (PDC) over 12 weeks(wk) for each Treatment Period(TP)

End point title	Change from Baseline in Day-time(AM) and Night-time (PM) Asthma Symptoms(Sy) from paper Diary Card (PDC) over 12 weeks(wk) for each Treatment Period(TP)
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End point description:

AM Sy scores were recorded nightly on PDC using scale:0=No Sy during day to 5=Sy so severe-could not go to work or perform normal daily activities. PM Sy scores were recorded every morning:0=No Sy during night to 4=Sy severe-did not sleep. BL= average of last 4 available of last 7 days of Screening Period(TP1) and of Washout Period(TP2). CFBL in average of daily scores=difference over 12 wks for each TP compared to BL. AM and PM Sy Scores were separately averaged over each of the two 12-wk TP. Total value of each endpoint over 12-wk TP was divided by number of days with non-missing data to obtain an average for each subject. Only par available at specified time points were analyzed (n=X, X in category titles). ITT population, Only those par available at the specified time points were analyzed (represented by n=X, X in the category titles). Par at each time point may have been different therefore a total of 82 par analyzed represents the overall ITT population.

End point type	Secondary
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End point timeframe:

Baseline and up to Day 85 of each Treatment Period

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82 ^[14]	82 ^[15]		
Units: Scores on the scale				
arithmetic mean (standard deviation)				
Day time (AM) score, n=81, 80	-0.38 (± 0.685)	-0.25 (± 0.706)		
Night time (PM) score, n= 81, 80	-0.16 (± 0.421)	-0.14 (± 0.389)		

Notes:

[14] - ITT population.

[15] - ITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the percentage of Symptom-Free days from paper Diary Card over 12 Weeks

End point title	Change from Baseline in the percentage of Symptom-Free days from paper Diary Card over 12 Weeks
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End point description:

A Symptom-Free day was defined as a 24-hour period with no symptoms recorded. Percentage of Symptom-Free Days was calculated dividing number of Symptom-Free days by the length of the Treatment Period. The baseline value of change from baseline in % of symptom free days is defined as an average of the last 7 available recorded values the Screening Period (for treatment period 1) and of the Washout Period (for treatment period 2). Change from Baseline was the difference in percentage of Symptom-Free days at week 12 compared to Baseline. The change from Baseline in the percentage of Symptom-Free days averaged over the 12-week Treatment Period was analyzed, using mixed effects ANCOVA model, with participant level Baseline percentage of Symptom-Free days, adjusted period-specific Baseline percentage of Symptom-Free days, treatment group and period as fixed effects and participant as a random effect.

End point type	Secondary
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End point timeframe:

Baseline and up to Day 85 of each Treatment Period

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81 ^[16]	80 ^[17]		
Units: Percentage of symptom-free days				
least squares mean (standard error)	11.36 ($\pm$ 2.852)	13.61 ($\pm$ 2.864)		

Notes:

[16] - ITT population, Only those participants available at the specified time points were analyzed.

[17] - ITT population, Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Multi-Dose DPI v FSC Capsule-Based Unit Dose DPI
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.97
upper limit	2.46

Secondary: Change from Baseline in Asthma Control Test (ACT) over 12 weeks for each treatment period

End point title	Change from Baseline in Asthma Control Test (ACT) over 12 weeks for each treatment period
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End point description:

The ACT is a 5-item questionnaire with a score of 1 to 5 for each item (1=poor control and 5=good control). The scores from each question were added to give an overall score. Baseline was defined as the value obtained predose (0 minutes) on day 1 of each Treatment Period. Change from Baseline was the difference in ACT score at the timepoint compared to Baseline score. The change from Baseline in overall ACT score was analysed, using mixed effects ANCOVA model, with participant level Baseline overall ACT score, adjusted period-specific Baseline overall ACT score, treatment group and period as fixed effects and participant as a random effect.

End point type	Secondary
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End point timeframe:

Baseline and up to Day 85 of each Treatment Period

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	78 ^[18]	80 ^[19]		
Units: Scores on the scale				
least squares mean (standard error)	3 (± 0.35)	3.2 (± 0.35)		

Notes:

[18] - ITT population, Only those participants available at the specified time points were analyzed.

[19] - ITT population, Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Multi-Dose DPI v FSC Capsule-Based Unit Dose DPI
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.5

Secondary: Change from Baseline in the percentage (%) of rescue-free days over 12 weeks (from paper Diary Card) for each Treatment Period(TP)

End point title	Change from Baseline in the percentage (%) of rescue-free days over 12 weeks (from paper Diary Card) for each Treatment Period(TP)
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End point description:

A rescue-free day is defined as a 24-hour period with no rescue medication usage recorded (i.e. both the day-time and night-time numbers of puffs of Salbutamol/Albuterol are zero). Percentage of Rescue-Free Days was calculated over each 12-week Treatment Period, dividing the number of rescue-free days by the length of the TP. The BL value of change from BL in % rescue free days is defined as an average of the last 7 available recorded values the Screening Period (for treatment period 1) and of the Washout Period (for treatment period 2). Change from BL was the difference over 12 weeks for each treatment period compared to BL. The change from BL in the % of rescue medication-free days averaged over the

12-week TP was analyzed, using mixed effects ANCOVA model, with par level BL % of rescue-free days, adjusted period-specific BL % of rescue-free days treatment group and period as fixed effects and par as a random effect.

End point type	Secondary
End point timeframe:	
Baseline and up to Day 85 of each Treatment Period	

End point values	FSC Capsule-Based Unit Dose DPI	FSC Multi-Dose DPI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81 ^[20]	80 ^[21]		
Units: Percentage of rescue-free days				
least squares mean (standard error)	6.04 (± 2.391)	6.81 (± 2.4)		

Notes:

[20] - ITT population, Only those participants available at the specified time points were analyzed.

[21] - ITT population, Only those participants available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FSC Capsule-Based Unit Dose DPI v FSC Multi-Dose DPI
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.64
upper limit	3.11

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of administration of the study drug until the follow-up contact (up to Week 28).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the safety population, comprised of all participants randomised to treatment, who had received at least one dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	FSC Multi-Dose DPI
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Reporting group description:

Participants received one actuations of FSC (250/50 mcg) self administered BID (morning and evening) via multi-dose DPI plus one actuation of Placebo self administered BID (morning and evening) via capsule-based unit dose DPI in either of two treatment periods for 12 weeks. Treatment periods were separated by washout period of 3 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Reporting group title	FSC Capsule-Based Unit Dose DPI
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Reporting group description:

Participants received one actuation of Placebo self administered BID (morning and evening) via multi-dose DPI plus one actuation of FSC (250/50 mcg) self administered BID (morning and evening) via capsule-based unit dose DPI in either of two treatment periods for 12 weeks. Treatment periods were separated by washout period of 3 weeks. Salbutamol/albuterol was provided to use as rescue medication.

Serious adverse events	FSC Multi-Dose DPI	FSC Capsule-Based Unit Dose DPI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	0 / 82 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	FSC Multi-Dose DPI	FSC Capsule-Based Unit Dose DPI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 82 (18.29%)	13 / 82 (15.85%)	
Investigations			
Blood pressure increased			

subjects affected / exposed occurrences (all)	3 / 82 (3.66%) 6	0 / 82 (0.00%) 0	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	4 / 82 (4.88%) 6	5 / 82 (6.10%) 10	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	10 / 82 (12.20%) 34	9 / 82 (10.98%) 18	

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