



## Clinical trial results:

**A multicentre, randomised, double-blind, double dummy, parallel group study to compare the salmeterol/fluticasone propionate combination (SERETIDE™) at a dose of 50/100mcg twice daily and fluticasone propionate (FLIXOTIDE™) at a dose of 200mcg twice daily, both delivered via a dry powder inhaler (DISKUS™) for 12 weeks in asthma in children aged 4-11 years not controlled by inhaled corticosteroids alone at medium dose**

### Summary

EudraCT number	2005-002949-40
Trial protocol	LT NO ES SE LV BE IT DK
Global end of trial date	26 October 2006

### Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	31 May 2015

### Trial information

#### Trial identification

Sponsor protocol code	SAM104926
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00353873
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?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	08 January 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 October 2006
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The main objective of this study is to compare salmeterol/fluticasone propionate 50/100mcg bd with fluticasone propionate (FP) 200mcg bd on lung function in subjects that are not controlled when previously treated at medium daily doses of inhaled corticosteroids alone.

Protection of trial subjects:

All subjects were randomized to active treatment. Oral corticosteroid use was permitted to treat asthma exacerbations should they have occurred during the study. The protocol advised that subjects should contact the investigator/primary physician should they experience worsening asthma during the study. No blood draws were required for this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	France: 189
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Latvia: 38
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Lithuania: 46
Country: Number of subjects enrolled	Netherlands: 34
Country: Number of subjects enrolled	Poland: 66
Country: Number of subjects enrolled	Russian Federation: 121
Worldwide total number of subjects	584
EEA total number of subjects	463

Notes:

<b>Subjects enrolled per age group</b>	
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)	584
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 584 participants were screened and entered into a 4-week run-in period receiving fluticasone propionate (FP) 100 microgram (µg) dry powder inhaler (DISKUS) twice daily (BD) and inhaled salbutamol (sal) as required. The number of participants randomized was 321, and 303 participants received investigational product post randomization.

### Period 1

Period 1 title	Overall Study (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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Fluticasone Propionate 200 µg BD

Arm description:

Participants received one inhalation from dry powder inhaler A (FP 100 µg) and dry powder inhaler B (FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation metered dose inhaler (MDI) to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.

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

Dosage and administration details:

200 µg twice daily

<b>Arm title</b>	Salmeterol/Fluticasone Propionate 50/100 µg BD
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Arm description:

Participants received one inhalation from dry powder inhaler A (salmeterol/fluticasone propionate [SFC] 50/100 µg) and dry powder inhaler B (placebo for FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation MDI to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	Salmeterol/fluticasone propionate combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

50/100 µg twice daily

<b>Number of subjects in period 1<sup>[1]</sup></b>	<b>Fluticasone Propionate 200 µg BD</b>	<b>Salmeterol/Fluticasone Propionate 50/100 µg BD</b>
Started	153	150
Completed	147	147
Not completed	6	3
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	-
Decision of Principal Investigator	2	-
Exacerbation	1	-
Protocol deviation	1	2

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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: A total of 584 participants were screened and entered into a 4-week run-in period receiving fluticasone propionate (FP) 100 microgram (µg) dry powder inhaler (DISKUS) twice daily (BD) and inhaled salbutamol as required. The number of participants randomized was 321, and 303 participants received investigational product post randomization. These 303 participants are reported to be in the baseline period.

## Baseline characteristics

### Reporting groups

Reporting group title	Fluticasone Propionate 200 µg BD
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Reporting group description:

Participants received one inhalation from dry powder inhaler A (FP 100 µg) and dry powder inhaler B (FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation metered dose inhaler (MDI) to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.

Reporting group title	Salmeterol/Fluticasone Propionate 50/100 µg BD
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Reporting group description:

Participants received one inhalation from dry powder inhaler A (salmeterol/fluticasone propionate [SFC] 50/100 µg) and dry powder inhaler B (placebo for FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation MDI to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.

Reporting group values	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD	Total
Number of subjects	153	150	303
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	8 ± 2.01	8.1 ± 2	-
Gender categorical Units: Subjects			
Female	55	53	108
Male	98	97	195
Race, Customized Units: Subjects			
African American/African Heritage	3	2	5
White - Arabic/North African Heritage	4	4	8
White - White/Caucasian/European Heritage	146	144	290

## End points

### End points reporting groups

Reporting group title	Fluticasone Propionate 200 µg BD
Reporting group description: Participants received one inhalation from dry powder inhaler A (FP 100 µg) and dry powder inhaler B (FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation metered dose inhaler (MDI) to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.	
Reporting group title	Salmeterol/Fluticasone Propionate 50/100 µg BD
Reporting group description: Participants received one inhalation from dry powder inhaler A (salmeterol/fluticasone propionate [SFC] 50/100 µg) and dry powder inhaler B (placebo for FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation MDI to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.	

### Primary: Mean Change from Baseline in Morning Peak Expiratory Flow (PEF) Over 12 weeks in Intent-to-treat (ITT) population

End point title	Mean Change from Baseline in Morning Peak Expiratory Flow (PEF) Over 12 weeks in Intent-to-treat (ITT) population
End point description: PEF is the maximum flow generated during expiration, as measured with a peak flow meter and recorded in electronic diary record card (eDRC), performed with maximal force and started after a full inspiration. The mean morning PEF measurement was constructed by calculating a simple mean for each participant over the interval Weeks 1 to 12. All PEF measurements were converted to the Wright/McKerow peak flow meter scale for the purposes of analyses. The change from baseline is then calculated by subtracting the baseline PEF values from the individual on-treatment values. Baseline was calculated as the mean of the values recorded on the seven days preceding randomization. The analysis was done using analysis of covariance (ANCOVA) adjusted for baseline PEF, country amalgamation, age, sex and treatment. ITT Population: all participants randomized to treatment who received at least one dose of randomized study medication.	
End point type	Primary
End point timeframe: Baseline; Week 1 up to Week 12	

End point values	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152 <sup>[1]</sup>	150 <sup>[2]</sup>		
Units: Liters/Minute (L/min)				
least squares mean (standard error)	19.3 (± 2.12)	26.9 (± 2.13)		

Notes:

[1] - ITT Population. Only participants with analyzable data at the indicated time point were assessed.

[2] - ITT Population. Only participants with analyzable data at the indicated time point were assessed.

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Fluticasone Propionate 200 µg BD v Salmeterol/Fluticasone Propionate 50/100 µg BD
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
P-value	= 0.012
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.6
Confidence interval	
level	95 %
sides	1-sided
lower limit	1.7

Notes:

[3] - Non-inferiority was tested using a one-sided significance level of 2.5%. If the lower confidence interval for the difference SFC-FP falls above -12 L/min the once daily SFC treatment combination was deemed to be statistically non-inferior. In the event that the lower confidence limit (2.5% 1-sided significance) exceeded 0, and using a separate closed testing procedure, superiority could be established.

### **Primary: Mean Change from Baseline in Morning PEF Over 12 weeks in Per Protocol (PP) population**

End point title	Mean Change from Baseline in Morning PEF Over 12 weeks in Per Protocol (PP) population
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End point description:

PEF is the maximum flow generated during expiration, as measured with a peak flow meter and recorded in eDRC, performed with maximal force and started after a full inspiration. The mean morning PEF measurement was constructed by calculating a simple mean for each participant over the interval Weeks 1 to 12. All PEF measurements were converted to the Wright/McKerow peak flow meter scale for the purposes of analyses. The change from baseline is then calculated by subtracting the baseline PEF values from the individual on-treatment values. Baseline was calculated as the mean of the values recorded on the seven days preceding randomization. The analysis was done using ANCOVA adjusted for baseline PEF, country amalgamation, age, sex and treatment. PP population: all participants in the ITT Population who did not have any protocol violations which could impact treatment effect.

End point type	Primary
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End point timeframe:

Baseline; Week 1 up to Week 12

<b>End point values</b>	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135 <sup>[4]</sup>	127 <sup>[5]</sup>		
Units: Liters/Minute				
least squares mean (standard error)	18.4 (± 2.14)	27.7 (± 2.21)		

Notes:

[4] - PP Population. Only participants with analyzable data at the indicated time point were assessed.

[5] - PP Population. Only participants with analyzable data at the indicated time point were assessed.

### **Statistical analyses**



<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Fluticasone Propionate 200 µg BD v Salmeterol/Fluticasone Propionate 50/100 µg BD
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[6]</sup>
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.3
Confidence interval	
level	95 %
sides	1-sided
lower limit	3.2

Notes:

[6] - Non-inferiority was tested using a one-sided significance level of 2.5%. If the lower confidence interval for the difference SFC-FP falls above -12 L/min the once daily SFC treatment combination was deemed to be statistically non-inferior. In the event that the lower confidence limit (2.5% 1-sided significance) exceeded 0, and using a separate closed testing procedure, superiority could be established.

## Secondary: Number of Participants who Achieved 'Totally Controlled' Asthma

End point title	Number of Participants who Achieved 'Totally Controlled' Asthma
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End point description:

Totally Controlled (TC) asthma is defined as no daily symptoms, no night-time waking due to asthma, no exacerbations, no rescue sal/albuterol use, no emergency visits,  $\geq 80\%$  predicted morning PEF, and no treatment related adverse events enforcing a change in asthma therapy over 7 consecutive days. Number of participants/group who achieved the status of at least TC during the last 8 weeks (wks) of treatment was analysed using logistic regression, including covariates for sex, age, treatment group, country amalgamation and baseline pre-bronchodilator forced expiratory volume in one second (FEV1). Asthma control was assessed each week for the last 8 wks of treatment period. Each week was classified as 'Totally Controlled', 'Well Controlled', 'Not Controlled' or 'Unevaluable'. A subject was considered to have TC asthma if they achieved 4/4, 5/5, 6/6, 6/7, 7/8 or 8/8 wks that were TC. 'Unevaluable' classification included subjects with less than 4 wks of data during the assessment period.

End point type	Secondary
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End point timeframe:

Week 5 up to Week 12

End point values	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152 <sup>[7]</sup>	150 <sup>[8]</sup>		
Units: Participants	23	28		

Notes:

[7] - ITT Population. Only participants with analyzable data at the indicated time point were assessed.

[8] - ITT Population. Only participants with analyzable data at the indicated time point were assessed.

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Fluticasone Propionate 200 µg BD v Salmeterol/Fluticasone

	Propionate 50/100 µg BD
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.389
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.4

### Secondary: Number of Participants who Achieved 'Well Controlled' Asthma

End point title	Number of Participants who Achieved 'Well Controlled' Asthma
End point description:	
Well Controlled (WC) asthma is defined as two or more of symptom score >1 only allowed on ≤2 days/week, rescue salbutamol/albuterol use on ≤2 days/week and up to a maximum of 4 times per week, ≥80% predicted morning PEF daily assessed for 7 consecutive days and all the following criteria: no night-time awakening due to asthma, no exacerbations, no emergency visits, no treatment related adverse events enforcing a change in any asthma therapy. Number of participants/group who achieved the status of at least WC during the last 8 wks of treatment was analysed using logistic regression, including covariates for sex, age, treatment group, country amalgamation and baseline pre-bronchodilator FEV1. Each week was classified as 'Well Controlled', 'Not Controlled' or 'Unevaluable'. A subject was considered to have WC asthma if they achieved 4/4, 5/5, 6/6, 6/7, 7/8 or 8/8 wks that were WC. 'Unevaluable' classification included subjects with less than 4 wks of data during the assessment period.	
End point type	Secondary
End point timeframe:	
Week 5 up to Week 12	

End point values	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152 <sup>[9]</sup>	150 <sup>[10]</sup>		
Units: Participants	61	65		

Notes:

[9] - ITT Population. Only participants with analyzable data at the indicated time point were assessed.

[10] - ITT Population. Only participants with analyzable data at the indicated time point were assessed.

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone Propionate 200 µg BD v Salmeterol/Fluticasone Propionate 50/100 µg BD

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.535
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.9

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the first day of treatment until the last day of treatment (up to 12 weeks).

Adverse event reporting additional description:

On-treatment SAEs and non-serious adverse events were reported for ITT Population, composed of all participants randomized to treatment who received at least one dose of randomized study medication.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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### Reporting groups

Reporting group title	Fluticasone Propionate 200 µg BD
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Reporting group description:

Participants received one inhalation from dry powder inhaler A (FP 100 µg) and dry powder inhaler B (FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation metered dose inhaler (MDI) to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.

Reporting group title	Salmeterol/Fluticasone Propionate 50/100 µg BD
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Reporting group description:

Participants received one inhalation from dry powder inhaler A (salmeterol/fluticasone propionate [SFC] 50/100 µg) and dry powder inhaler B (placebo for FP 100 µg) twice-daily, in the morning and evening for 12 weeks. Participants were provided salbutamol 100 µg per actuation MDI to be used as needed throughout the study, for prevention of exercise induced asthma and symptomatic relief from asthma symptoms.

<b>Serious adverse events</b>	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 153 (1.96%)	3 / 150 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 153 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 153 (0.65%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Laryngotracheitis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Fluticasone Propionate 200 µg BD	Salmeterol/Fluticasone Propionate 50/100 µg BD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 153 (39.87%)	55 / 150 (36.67%)	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 153 (15.03%)	27 / 150 (18.00%)	
occurrences (all)	33	81	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 153 (3.92%)	8 / 150 (5.33%)	
occurrences (all)	7	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 153 (6.54%)	7 / 150 (4.67%)	
occurrences (all)	13	7	
Rhinitis allergic			
subjects affected / exposed	10 / 153 (6.54%)	6 / 150 (4.00%)	
occurrences (all)	12	12	

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	19 / 153 (12.42%) 25	14 / 150 (9.33%) 15	
Rhinitis subjects affected / exposed occurrences (all)	10 / 153 (6.54%) 15	12 / 150 (8.00%) 15	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported