



Clinical trial results:

A 26 week, randomized, active-controlled safety study of double-blind formoterol

fumarate in free combination with an inhaled corticosteroid versus an inhaled corticosteroid in

adolescent and adult patients with persistent asthma

Summary

EudraCT number	2012-004854-27
Trial protocol	GB LT SE LV HU EE FI DK ES SK PL
Global end of trial date	10 May 2016

Results information

Result version number	v1
This version publication date	25 November 2016
First version publication date	25 November 2016

Trial information

Trial identification

Sponsor protocol code	CFOR258D2416
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01845025
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	10 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that the addition of formoterol fumarate (FOM) to fluticasone propionate (FP) therapy is non-inferior to FP therapy alone in terms of the risk of composite serious asthma-related events (asthma-related hospitalization, asthma-related intubation and asthma-related death).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2013
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	United States: 820
Worldwide total number of subjects	820
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	69
Adults (18-64 years)	646
From 65 to 84 years	105

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Following the decision to stop further enrollment into the study, 1121 patients had been screened, of whom 825 were randomized. Of the 820 patients randomized and treated and part of Intent To Treat (ITT analysis) 5 patients were randomized but were excluded from the ITT analyses as they did not take study medication.

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
Arm title	FOM 12 mcg + FP

Arm description:

Formoterol 12 mcg + fluticasone propionate 100 mcg, 250 mcg or 500 mcg for inhalation

Arm type	Experimental
Investigational medicinal product name	Formoterol (FOM)
Investigational medicinal product code	FOR258
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Formoterol (FOM) 12 µg capsules in dry powder inhaler in the morning and evening for 26 weeks

Investigational medicinal product name	fluticasone propionate (FP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

fluticasone propionate (FP) 100 mcg, 250 mcg or 500 mcg capsules in dry powder inhaler in the morning and evening for 26 weeks

Arm title	fluticasone propionate (FP)
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Arm description:

fluticasone propionate 100 mcg, 250 mcg or 500 mcg + Placebo to Match Formoterol 12 mcg for inhalation

Arm type	Active comparator
Investigational medicinal product name	fluticasone propionate (FP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

fluticasone propionate (FP) 100 mcg, 250 mcg or 500 mcg capsules in dry powder inhaler in the morning and evening for 26 weeks

Investigational medicinal product name	Placebo to match Formoterol
Investigational medicinal product code	FOR258
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Placebo to Match Formoterol (FOM) capsules in dry powder inhaler in the morning and evening for 26 weeks

Number of subjects in period 1	FOM 12 mcg + FP	fluticasone propionate (FP)
Started	411	409
Completed	326	332
Not completed	85	77
Adverse event, serious fatal	2	-
Consent withdrawn by subject	48	44
Adverse event, non-fatal	6	3
Unsatisfactory therapeutic effect	4	2
Protocol deviation	3	6
Administrative problems	8	8
Lost to follow-up	13	13
Missing	1	1

Baseline characteristics

Reporting groups

Reporting group title	FOM 12 mcg + FP
Reporting group description: Formoterol 12 mcg + fluticasone propionate 100 mcg, 250 mcg or 500 mcg for inhalation	
Reporting group title	fluticasone propionate (FP)
Reporting group description: fluticasone propionate 100 mcg, 250 mcg or 500 mcg + Placebo to Match Formoterol 12 mcg for inhalation	

Reporting group values	FOM 12 mcg + FP	fluticasone propionate (FP)	Total
Number of subjects	411	409	820
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
Adolescents (12-17 years)	37	32	69
Adults (18-64 years)	327	319	646
From 65-84 years	47	58	105
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	44.7	45.6	
standard deviation	± 16.67	± 17.02	-
Gender, Male/Female Units: Subjects			
Male	127	137	264
Female	284	272	556

End points

End points reporting groups

Reporting group title	FOM 12 mcg + FP
Reporting group description: Formoterol 12 mcg + fluticasone propionate 100 mcg, 250 mcg or 500 mcg for inhalation	
Reporting group title	fluticasone propionate (FP)
Reporting group description: fluticasone propionate 100 mcg, 250 mcg or 500 mcg + Placebo to Match Formoterol 12 mcg for inhalation	

Primary: time to the first occurrence of any composite endpoint including asthma-related hospitalizations, intubations and deaths during the study at 26 weeks

End point title	time to the first occurrence of any composite endpoint including asthma-related hospitalizations, intubations and deaths during the study at 26 weeks ^[1]
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End point description:

The primary safety endpoint was the time to the first occurrence of any composite endpoint. The composite events include asthma-related deaths, asthma-related intubations and asthma-related hospitalizations. The number of events includes all adjudication confirmed events, one patient could experience multiple events during the course of study; Event rate = $100 * n$ patients with any events / total N patients in treatment group.

End point type	Primary
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End point timeframe:

26 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome as this is a safety outcome.

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: participants				
Composite event	3	3		
Asthma-related death	0	0		
Asthma-related intubation	0	0		
Asthma-related hospitalization	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of asthma exacerbations at 26 weeks

End point title	Number of asthma exacerbations at 26 weeks
End point description: Number of asthma exacerbations events	
End point type	Secondary

End point timeframe:

26 weeks

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: events				
arithmetic mean (standard deviation)	1.3 (± 0.62)	1.2 (± 0.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days of School/Work Missed at 26 weeks

End point title	Percentage of days of School/Work Missed at 26 weeks
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End point description:

The percentage of days of school/work missed during the treatment period (26 weeks). Overall percentage of school days missed for each student patient or of work days missed is calculated by total number of days missed divided by total days of treatment.

End point type	Secondary
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End point timeframe:

26 weeks

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: days				
arithmetic mean (standard deviation)	0.97 (± 4.558)	0.56 (± 1.641)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days with limited ability to perform normal daily activities at 26 weeks

End point title	Percentage of days with limited ability to perform normal daily activities at 26 weeks
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End point description:

The percentage of days with limited ability to perform normal daily activities during the treatment period (26 weeks). Percentage is calculated as total number of days when the patient had limited ability to perform normal daily activities divided by total days of treatment.

End point type	Secondary
End point timeframe:	
26 weeks	

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: days				
arithmetic mean (standard deviation)	4.73 (\pm 12.774)	4.75 (\pm 12.705)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days with nighttime awakenings at 26 weeks

End point title	Percentage of days with nighttime awakenings at 26 weeks
End point description:	
Percentage of days with nighttime awakenings during the treatment period (26 weeks)	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: days				
arithmetic mean (standard deviation)	4.55 (\pm 9.577)	4.2 (\pm 8.956)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days with no rescue medication use at 26 weeks

End point title	Percentage of days with no rescue medication use at 26 weeks
End point description:	
Percentage of rescue free days is calculated as total number of days with no rescue medication was taken divided by total days of treatment.	
End point type	Secondary

End point timeframe:

26 weeks

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: days				
arithmetic mean (standard deviation)	76.97 (± 27.255)	73.29 (± 30.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of days with no symptoms at 26 weeks

End point title	Percentage of days with no symptoms at 26 weeks
End point description: Percentage of days with no symptoms during the treatment period (26 weeks). Percentage is calculated as total number of days with no symptoms divided by total days of treatment.	
End point type	Secondary
End point timeframe: 26 weeks	

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: days				
arithmetic mean (standard deviation)	79.47 (± 25.501)	77.64 (± 28.394)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma control Questionnaire (ACQ – 6) score at week 26

End point title	Change from baseline in Asthma control Questionnaire (ACQ – 6) score at week 26
End point description: Change from baseline in Asthma control Questionnaire (ACQ – 6) score at week 26. Results of the Asthma control questionnaire (ACQ-6); The average score of the six questions is calculated as the sum of scores divided by the number of questions that were answered at the time point, as long as there	

were at least 4 questions answered. The ACQ6 score is calculated as the mean of the responses to the first 6 questions of the ACQ. The ACQ is a scale containing 7 questions, each question has a 7-point scale which ranges from 0 to 6; a score of 0 corresponds to no impairment and a score of 6 corresponds to maximum impairment.

End point type	Secondary
End point timeframe:	
baseline and 26 weeks	

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.65 (± 1.224)	-0.59 (± 1.094)		

Statistical analyses

No statistical analyses for this end point

Secondary: Unplanned healthcare utilization at Visit 3, Visit 4 and Visit 5

End point title	Unplanned healthcare utilization at Visit 3, Visit 4 and Visit 5
End point description:	
Unplanned healthcare utilization by visit (Telephone contact with study doctor (MD); Telephone contact with other physician (MD) or healthcare provider (HCP); Unscheduled or unplanned visit to study doctor (including home visits); Unscheduled or unplanned visit to other physician or healthcare provider (including home visits); Emergency department or hospital visit (< 24 hours); Hospital admission or Emergency department visit (> 24 hours).	
End point type	Secondary
End point timeframe:	
Visit 3, Visit 4 and Visit 5	

End point values	FOM 12 mcg + FP	fluticasone propionate (FP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	409		
Units: unplanned visits				
Telephone contact with study MD: V3	19	18		
Telephone contact with other MD or HCP: V3	5	9		
unplanned visit to study MD;include home:V3	7	13		
unplanned visit to other MD or HCP incl.home:V3	5	9		
Emergency or hospital visit (< 24 hours):V3	3	4		
Hospital admission or Emergency visit (>24hrs):V3	1	1		

Telephone contact with study MD: V4	25	17		
Telephone contact with other MD or HCP: V4	5	7		
unplanned visit to study MD;include home:V4	10	15		
unplanned visit to other MD or HCP incl.home:V4	15	16		
Emergency or hospital visit (< 24 hours):V4	3	4		
Hospital admission or Emergency visit (>24hrs):V4	0	2		
Telephone contact with study MD: V5	14	9		
Telephone contact with other MD or HCP: V5	8	2		
unplanned visit to study MD;include home:V5	6	9		
unplanned visit to other MD or HCP incl.home:V5	10	7		
Emergency or hospital visit (< 24 hours):V5	4	6		
Hospital admission or Emergency visit (>24hrs):V5	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	FOM 12 mcg + FP
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Reporting group description:

Formoterol 12 mcg + fluticasone propionate 100 mcg, 250 mcg or 500 mcg for inhalation

Reporting group title	fluticasone propionate (FP)
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Reporting group description:

fluticasone propionate 100 mcg, 250 mcg or 500 mcg + Placebo to Match Formoterol 12 mcg for inhalation

Serious adverse events	FOM 12 mcg + FP	fluticasone propionate (FP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 411 (2.43%)	9 / 409 (2.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Alcohol poisoning			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Presyncope			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 411 (0.49%)	2 / 409 (0.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 411 (0.49%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 411 (0.24%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 411 (0.24%)	0 / 409 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 409 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FOM 12 mcg + FP	fluticasone propionate (FP)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 411 (1.22%)	9 / 409 (2.20%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	5 / 411 (1.22%)	9 / 409 (2.20%)	
occurrences (all)	7	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2015	Amendment 1: Clarified inclusion of women of child-bearing potential. Clarified exclusion of patients with history of malignancy and cardiovascular conditions. Clarified that contacting the medical monitor was not mandatory before unblinding. Added assessment of pharmacogenetic sampling and the timing of sampling with respect to the visit schedule, details of the sampling technique and the analysis plan. Clarified the sample size calculation and non-inferiority margin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the action to withdraw the Foradil Aerolizer NDA in US; study was discontinued. This was a commercial reason and not due to any change in benefit-risk.

Notes: