Clinical trial results:
A Phase IIa, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety and Efficacy of 28 Day Oral Administration of BAY 85-8501 in Patients with non-Cystic Fibrosis Bronchiectasis

Summary

EudraCT number	2012-004491-18
Trial protocol	GB ES IT
Global end of trial date	13 June 2014

Results information

Result version number	v2 (current)
This version publication date	03 September 2016
First version publication date	24 July 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY85-8501 / 16359

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01818544
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 28 day oral administration of BAY 85-8501 versus placebo in subjects with non-Cystic Fibrosis (CF) Bronchiectasis (BE).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Italy: 54
Worldwide total number of subjects	94
EEA total number of subjects	94

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 27 sites in 4 countries between 22 April 2013 (first subject first visit) and 13 June 2014 (last subject last visit).

Pre-assignment

Screening details:

Of 139 subjects screened, 94 subjects were randomized to the study. The reason for 45 screen failures was non-fulfilment of the inclusion or exclusion and subject withdrawal criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY85-8501

Arm description:

Daily oral dose of 1 milligram (mg) BAY85-8501 tablets for 28 days.

Arm type	Experimental
Investigational medicinal product name	BAY85-8501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daily oral dose of 1 mg BAY85-8501 tablets for 28 days.

Arm title	Placebo

Arm description:

Placebo matched to BAY85-8501 for 28 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to BAY85-8501 for 28 days.

Number of subjects in period 1	BAY85-8501	Placebo
Started	47	47
Treated	45	47
Completed	37	45
Not completed	10	2
Consent withdrawn by subject	1	-
Protocol violation	2	-
Adverse event	6	1
Unspecified	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BAY85-8501
Reporting group description:	
Daily oral dose of 1 milligram (mg) BAY85-8501 tablets for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to BAY85-8501 for 28 days.	

Reporting group values	BAY85-8501	Placebo	Total
Number of subjects	47	47	94
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	64.1	68.6	
standard deviation	± 12.21	± 8.04	-
Gender categorical Units: Subjects			
Female	22	22	44
Male	25	25	50

End points

End points reporting groups

Reporting group title	BAY85-8501
Reporting group description:	
Daily oral dose of 1 milligram (mg) BAY85-8501 tablets for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to BAY85-8501 for 28 days.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population (N= 92) was defined as all subjects who received at least one dose of study medication.	
Subject analysis set title	Full Analysis Set (FAS) Population
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS population (N= 94) was defined as all randomized subjects.	

Primary: Number Of Subjects Who Need To Discontinue Study Medication Due To Findings In Physical Examination

End point title	Number Of Subjects Who Need To Discontinue Study Medication Due To Findings In Physical Examination[1]
End point description:	
End point type	Primary
End point timeframe:	
From start of study treatment up to follow-up visit (28 days after last dose)	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[2]	47[3]		
Units: Subjects	4	1		

Notes:

[2] - Safety population

[3] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Systolic Blood Pressure At Days 7, 14, 21, 28, 56

End point title	Change From Baseline in Systolic Blood Pressure At Days 7, 14, 21, 28, 56[4]
End point description:	
In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.	
End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[4] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[5]	47[6]		
Units: millimeter of mercury				
arithmetic mean (standard deviation)				
Baseline (N= 45, 47)	134.6 (± 21.48)	133.1 (± 16.94)		
Change at Day 7 (N= 43, 47)	1.1 (± 13.75)	0.8 (± 12.68)		
Change at Day 14 (N= 42, 46)	-1.4 (± 14.64)	-1.1 (± 14.34)		
Change at Day 21 (N= 42, 47)	-3.4 (± 15.93)	-1 (± 13.03)		
Change at Day 28 (N= 44, 47)	-3.6 (± 13.13)	-2.9 (± 16.21)		
Change at Day 56 (N= 39, 46)	-3 (± 15.37)	-2 (± 13.17)		

Notes:

[5] - Safety population

[6] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Diastolic Blood Pressure At Days 7, 14, 21, 28, 56

End point title	Change From Baseline in Diastolic Blood Pressure At Days 7, 14, 21, 28, 56[7]

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[7] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[8]	47[9]		
Units: millimeter of mercury				
arithmetic mean (standard deviation)				
Baseline (N= 45, 47)	76.9 (± 10.81)	77.3 (± 11.32)		
Change at Day 7 (N= 43, 47)	-0.7 (± 8.39)	-3.6 (± 9.29)		
Change at Day 14 (N= 42, 46)	-2.4 (± 10.19)	-2.3 (± 8.67)		
Change at Day 21 (N= 42, 47)	-1.1 (± 8.43)	-2 (± 9.14)		
Change at Day 28 (N= 44, 47)	-2 (± 7.99)	-3.7 (± 9.43)		
Change at Day 56 (N= 39, 46)	-2.5 (± 9.67)	-3.8 (± 8.97)		

Notes:

[8] - Safety population

[9] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Heart Rate At Days 7, 14, 21, 28, 56

End point title	Change From Baseline in Heart Rate At Days 7, 14, 21, 28,

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[10] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[11]	47[12]		
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline (N= 45, 47)	74.6 (± 10.82)	74.5 (± 10.6)		
Change at Day 7 (N= 43, 47)	0.5 (± 9.35)	-0.4 (± 11.06)		
Change at Day 14 (N= 42, 46)	-2.2 (± 8.28)	0.2 (± 9.5)		
Change at Day 21 (N= 42, 47)	0.2 (± 10.93)	1.5 (± 10.96)		
Change at Day 28 (N= 44, 47)	-0.7 (± 10.09)	1 (± 10.8)		
Change at Day 56 (N= 39, 46)	-1.9 (± 12.46)	1.7 (± 8.57)		

Notes:

[11] - Safety population

[12] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With new Abnormal (Pathologic) Electrocardiogram (ECG) Findings From Baseline to Day 28

End point title	Number of Subjects With new Abnormal (Pathologic) Electrocardiogram (ECG) Findings From Baseline to Day 28[13]

End point description:

ECG abnormalities that were considered clinically significant (CS) or clinically insignificant (CI) by the investigator were reported. Parameters analyzed included ventricular rate, PR duration, QRS duration, and QT duration to the subjects.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28

Notes:

[13] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[14]	47[15]		
Units: Subjects				
Baseline: Abnormal, CI	6	14		
Baseline: Abnormal, CS	0	0		
Change at Day 7: Abnormal, CI	4	12		
Change at Day 7: Abnormal, CS	0	0		
Change at Day 14: Abnormal, CI	6	16		
Change at Day 14: Abnormal, CS	0	1		
Change at Day 21: Abnormal, CI	5	14		
Change at Day 21: Abnormal, CS	0	0		
Change at Day 28: Abnormal, CI	7	13		
Change at Day 28: Abnormal, CS	0	0		

Notes:

[14] - Safety population

[15] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Show Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TB) Abnormalities in Their Safety Lab Assessment

End point title	Number of Subjects who Show Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TB) Abnormalities in Their Safety Lab Assessment[16]

End point description:

The pre-specified laboratory abnormalities included ALT and AST greater than or equal to (>=) 3 times upper limit of normal (ULN) and total bilirubin with an increase of 200% from baseline.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[16] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[17]	45[18]		
Units: Subjects				
Baseline (ALT)	1	0		
Change at Day 7 (ALT)	0	0		
Change at Day 14 (ALT)	0	0		
Change at Day 21 (ALT)	0	0		
Change at Day 28 (ALT)	0	1		

Change at Day 56 (ALT)	0	0		
Baseline (AST)	0	0		
Change at Day 7 (AST)	0	1		
Change at Day 14 (AST)	0	0		
Change at Day 21 (AST)	0	0		
Change at Day 28 (AST)	0	0		
Change at Day 56 (AST)	0	0		
Change at Day 7 (TB)	0	1		
Change at Day 14 (TB)	0	0		
Change at Day 21 (TB)	1	0		
Change at Day 28 (TB)	0	1		
Change at Day 56 (TB)	0	0		

Notes:

[17] - Safety Population

[18] - Safety population

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Drug-Related Adverse Events as a Measure of Safety And Tolerability

End point title	Number of Subjects With Drug-Related Adverse Events as a Measure of Safety And Tolerability[19]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent adverse events were defined as adverse events/serious adverse events that started or worsened after the start of study drug administration.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[19] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[20]	47[21]		
Units: Subjects				
Any Study Drug Related TEAE	11	12		
Any Study Drug Related Serious TEAE	0	0		

Notes:

[20] - Safety population

[21] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Function Test Forced Expired

Volume in 1 Second (FEV1) At Days 7, 14, 21, 28, 56

End point title	Change From Baseline in Pulmonary Function Test Forced Expired Volume in 1 Second (FEV1) At Days 7, 14, 21, 28, 56

End point description:

FEV1 is a pulmonary function test, defined as the amount of air expelled in 1 second, included pre-bronchodilator (BD) and post-bronchodilator (BD) tests. The pre-BDs were performed prior to administration of any BD where as post-BDs were obtained within at least 15 minutes and no more than 30 minutes after administration of standard dose of BD. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[22]	47[23]		
Units: liters				
arithmetic mean (standard deviation)				
Baseline Pre-bronchodialator (BD) (N= 39, 44)	1.631 (± 0.6687)	1.448 (± 0.4387)		
Baseline Post-BD (N= 44, 47)	1.705 (± 0.5875)	1.522 (± 0.4489)		
Change at Day 7: Pre-BD (N= 37, 44)	-0.01 (± 0.1331)	-0.007 (± 0.1153)		
Change at Day 7: Post-BD (N= 43, 47)	0.01 (± 0.1526)	0.004 (± 0.1343)		
Change at Day 14: Pre-BD (N= 36, 43)	0.018 (± 0.1617)	-0.03 (± 0.1528)		
Change at Day 14: Post-BD (N= 42, 46)	0.035 (± 0.1698)	-0.028 (± 0.1798)		
Change at Day 21: Pre-BD (N= 36, 44)	-0.024 (± 0.1534)	-0.075 (± 0.156)		
Change at Day 21: Post-BD (N= 42, 47)	0.016 (± 0.137)	-0.032 (± 0.1637)		
Change at Day 28: Pre-BD (N= 37, 44)	-0.004 (± 0.1552)	-0.078 (± 0.1986)		
Change at Day 28: Post-BD (N= 42, 47)	0.026 (± 0.1924)	-0.051 (± 0.197)		
Change at Day 56: Pre-BD (N= 34, 43)	-0.014 (± 0.1541)	-0.063 (± 0.2214)		
Change at Day 56: Post-BD (N= 39, 45)	-0.026 (± 0.174)	-0.073 (± 0.2101)		

Notes:

[22] - FAS population

[23] - FAS population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

FEV1 was analyzed by an analysis of covariance (ANCOVA) with baseline as a covariate and treatment as a factor. Adjusted means (least square [LS] means) for treatment, as well as the difference in LS means between treatment groups, and the corresponding 95% confidence intervals were calculated.

Comparison groups	BAY85-8501 v Placebo

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0558
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0021
upper limit	0.1653

Secondary: Change From Baseline in Pulmonary Function Test Forced Vital Capacity (FVC) at Days 7, 14, 21, 28, 56

End point title	Change From Baseline in Pulmonary Function Test Forced Vital Capacity (FVC) at Days 7, 14, 21, 28, 56

End point description:

FVC is defined as the total amount of air exhaled during the lung function test. FVC is a pulmonary function test included pre-bronchodilator and post-bronchodilator tests. The pre-BDs were performed prior to administration of any BD where as post-BDs were obtained within at least 15 minutes and no more than 30 minutes after administration of standard dose of BD. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[24]	47[25]		
Units: liters				
arithmetic mean (standard deviation)				
Baseline Pre-BD (N= 39, 44)	2.733 (± 1.0127)	2.46 (± 0.7168)		
Baseline Post-BD (N= 44, 47)	2.819 (± 0.9748)	2.529 (± 0.673)		
Change at Day 7: Pre-BD (N= 37, 44)	0.008 (± 0.2387)	-0.003 (± 0.2294)		
Change at Day 7: Post-BD (N= 43, 47)	0.031 (± 0.2422)	0.007 (± 0.2397)		
Change at Day 14: Pre-BD (N= 36, 43)	0.026 (± 0.2193)	-0.044 (± 0.2678)		
Change at Day 14: Post-BD (N= 42, 46)	0.072 (± 0.257)	0 (± 0.1924)		
Change at Day 21: Pre-BD (N= 36, 44)	-0.01 (± 0.2658)	-0.073 (± 0.2227)		
Change at Day 21: Post-BD (N= 42, 47)	0.077 (± 0.2832)	-0.031 (± 0.2377)		
Change at Day 28: Pre-BD (N= 37, 44)	-0.009 (± 0.2997)	-0.06 (± 0.2495)		

Change at Day 28: Post-BD (N= 42, 47)	0.013 (± 0.3402)	-0.029 (± 0.2086)		
Change at Day 56: Pre-BD (N= 34, 43)	-0.04 (± 0.2676)	-0.04 (± 0.3101)		
Change at Day 56: Post-BD (N= 39, 45)	0.007 (± 0.3405)	-0.03 (± 0.2734)		

Notes:

[24] - FAS population

[25] - FAS population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

FVC was analyzed by an ANCOVA with baseline as a covariate and treatment as a factor. Adjusted means (LS means) for treatment, as well as the difference in LS means between treatment groups, and the corresponding 95% confidence intervals were calculated.

Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3993
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0686
upper limit	0.1704

Secondary: Change From Baseline in Pulmonary Function Test Forced Expiratory Flow Over the Middle Half of Subject's Forced Vital Capacity (FVC) (FEF25-75) at Days 7, 14, 21, 28, 56

End point title	Change From Baseline in Pulmonary Function Test Forced Expiratory Flow Over the Middle Half of Subject's Forced Vital Capacity (FVC) (FEF25-75) at Days 7, 14, 21, 28, 56

End point description:

FEF 25 Percent (%)-75% measurement describes the amount of air expelled from the lungs during the middle half (25% - 75%) of the forced vital capacity test. FEF25-75 is a pulmonary function test included pre-BD and post-BDs. The pre-BDs were performed prior to administration of any BD where as post-BDs were obtained within at least 15 minutes and no more than 30 minutes after administration of standard dose of BD. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[26]	47[27]		
Units: liter per second				
arithmetic mean (standard deviation)				
Baseline: Pre-BD (N= 37, 43)	0.927 (± 0.7019)	0.79 (± 0.4473)		
Baseline: Post-BD (N= 41, 46)	0.96 (± 0.6376)	0.858 (± 0.4768)		
Change at Day 7: Pre-BD (N= 35, 43)	-0.021 (± 0.1989)	-0.033 (± 0.1622)		
Change at Day 7: Post-BD (N= 40, 46)	0.045 (± 0.3017)	-0.004 (± 0.2318)		
Change at Day 14: Pre-BD (N= 34, 42)	0.028 (± 0.3661)	-0.03 (± 0.2288)		
Change at Day 14: Post-BD (N= 39, 45)	0.064 (± 0.4494)	-0.023 (± 0.3312)		
Change at Day 21: Pre-BD (N= 34, 43)	-0.019 (± 0.2114)	-0.088 (± 0.2813)		
Change at Day 21: Post-BD (N= 39, 46)	-0.058 (± 0.3483)	-0.06 (± 0.2851)		
Change at Day 28: Pre-BD (N= 35, 43)	-0.045 (± 0.3533)	-0.103 (± 0.3242)		
Change at Day 28: Post-BD (N= 39, 46)	0.081 (± 0.4294)	-0.038 (± 0.3975)		
Change at Day 56: Pre-BD (N= 32, 42)	0.07 (± 0.3323)	-0.068 (± 0.3002)		
Change at Day 56: Post-BD (N= 36, 44)	-0.066 (± 0.5485)	-0.077 (± 0.4097)		

Notes:

[26] - FAS population

[27] - FAS population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

FEF25-75 was analyzed by an ANCOVA with baseline as a covariate and treatment as a factor. Adjusted means (LS means) for treatment, as well as the difference in LS means between treatment groups, and the corresponding 95% confidence intervals were calculated.

Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1159
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	0.138
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0348
upper limit	0.3114

Secondary: Change From Baseline in Total Score on St. George's Respiratory Questionnaire (SGRQ) at Day 28 and 56

End point title	Change From Baseline in Total Score on St. George's Respiratory Questionnaire (SGRQ) at Day 28 and 56

End point description:

SGRQ has been developed to measure the impact of respiratory disease on health status. The SGRQ scoring was done 0-100% with 0 being no impairment of quality of life. This was scored separately for each of 3 sections (Activity, Impact and Symptom) of the questionnaire and a summary score utilizing responses to all items was the total SGRQ score. This total score ranged from zero to 100%. Score range of change from baseline between -4 to +4 points indicate "no clinical relevant change"; less than (<) 4 points indicate "improvement"; greater than (>) 4 points indicate "deterioration". In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[28]	47[29]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline (N= 42, 46)	43.18 (± 20.159)	39.68 (± 14.546)		
Change at Day 28 (N= 40, 45)	0.36 (± 9.051)	0.18 (± 11.715)		
Change at Day 56 (N= 36, 44)	-0.87 (± 6.851)	1.54 (± 10.874)		

Notes:

[28] - FAS population

[29] - FAS population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Baseline value was defined as the last non-missing assessment prior to the first dose of study drug. Adjusted means was defined as LS means. Data at the EOT (Week 4/Day 28) visit analyzed by the ANCOVA with baseline as a covariate and treatment as a factor (BAY85-8501 versus placebo).

Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7028
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	0.862
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6172
upper limit	5.3412

Secondary: Change From Baseline in 24 Hours Sputum Weight at Day 28

End point title	Change From Baseline in 24 Hours Sputum Weight at Day 28

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 28

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[30]	47[31]		
Units: gram(s)				
arithmetic mean (standard deviation)				
Baseline (N= 45, 47)	22.14 (± 19.8151)	25.431 (± 24.4686)		
Change at Day 28 (N= 40, 44)	-0.126 (± 14.3549)	-3.398 (± 11.4987)		

Notes:

[30] - FAS population

[31] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Alpha-1 Antitrypsin Human Neutrophil Elastase (A1AH-NE) Complex, Interleukin-8 (IL-8)

End point title	Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Alpha-1 Antitrypsin Human Neutrophil Elastase (A1AH-NE) Complex, Interleukin-8 (IL-8)

End point description:

Sputum biomarker assessments were taken from induced sputum. Inflammatory markers, included IL-8, A1AH-NE complex were recorded. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[32]	47[33]		
Units: microgram per liter				
arithmetic mean (standard deviation)				
Baseline: A1AH-NE (N= 44, 47)	22.558 (± 19.408)	23 (± 37.4346)		
Change at Day 14: A1AH-NE (N= 38, 45)	0.62 (± 13.338)	13.482 (± 62.8838)		
Change at Day 28: A1AH-NE (N= 40, 45)	-4.805 (± 17.3091)	-1.803 (± 24.2774)		
Change at Day 56: A1AH-NE (N= 34, 42)	-1.985 (± 17.5933)	10.17 (± 43.4871)		
Baseline: IL-8 (N= 44, 47)	105.5 (± 112.305)	95.7 (± 91.279)		
Change at Day 14: IL-8 (N= 38, 45)	9.19 (± 59.909)	-6.73 (± 52.883)		
Change at Day 28: IL-8 (N= 40, 46)	13.14 (± 58.059)	-12.19 (± 51.165)		
Change at Day 56: IL-8 (N= 34, 42)	20.66 (± 62.955)	-1.42 (± 73.201)		

Notes:

[32] - FAS population

[33] - FAS population

Statistical analyses

Statistical analysis title	Alpha-1-antitrypsin Human NE Complex in Sputum
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.311
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	-2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.475
upper limit	2.732

Statistical analysis title	Interleukin-8 in Sputum
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0215
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	27.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.093
upper limit	50.021

Secondary: Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Neutrophil cell Count

End point title	Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Neutrophil cell Count

End point description:

Sputum biomarker assessments were taken from induced sputum. Inflammatory markers, included neutrophil cell count. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[34]	47[35]		
Units: giga per liter				
arithmetic mean (standard deviation)				
Baseline (N= 41, 39)	17.76 (± 21.3226)	20.107 (± 25.2439)		
Change at Day 14 (N= 32, 34)	-0.301 (± 17.1693)	-0.11 (± 16.0611)		
Change at Day 28 (N= 36, 36)	-3.446 (± 12.6294)	0.786 (± 27.9962)		
Change at Day 56 (N= 25, 34)	-0.513 (± 12.5183)	-2.067 (± 23.12)		

Notes:

[34] - FAS population

[35] - FAS population

Statistical analyses

Statistical analysis title	Neutrophil cell Count in Sputum
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3704
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	-4.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.463
upper limit	5.46

Secondary: Change From Baseline of Human Neutrophil Elastase (NE) Activity in Sputum at Days 14, 28, 56

End point title	Change From Baseline of Human Neutrophil Elastase (NE) Activity in Sputum at Days 14, 28, 56

End point description:

Neutrophil elastase activity in sputum was performed to treatment group for each scheduled visit. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[36]	47[37]		
Units: units per liter				
arithmetic mean (standard deviation)				
Baseline (N= 44, 47)	213.21 (± 229.235)	250.21 (± 296.335)		
Change at Day 14 (N= 38, 45)	34.62 (± 170.219)	-22.29 (± 137.516)		
Change at Day 28 (N= 40, 46)	-6.76 (± 169.055)	-24.84 (± 155.737)		
Change at Day 56 (N= 34, 42)	11.89 (± 162.026)	-41 (± 216.065)		

Notes:

[36] - FAS population

[37] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Human Neutrophil Elastase (NE) Concentration in Sputum at Days 14, 28, 56

End point title	Change From Baseline of Human Neutrophil Elastase (NE) Concentration in Sputum at Days 14, 28, 56

End point description:

Neutrophil elastase concentration in sputum was performed to treatment group for each scheduled visit. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[38]	47[39]		
Units: microgram per liter				
arithmetic mean (standard deviation)				
Baseline (N= 44, 47)	24.567 (± 37.7496)	39.215 (± 120.0264)		
Change at Day 14 (N= 38, 45)	21.261 (± 20.4157)	32.79 (± 91.6294)		
Change at Day 28 (N= 40, 44)	-7.59 (± 33.8392)	-12.523 (± 112.9358)		
Change at Day 56 (N= 34, 42)	-2.282 (± 35.3634)	16.033 (± 190.0303)		

Notes:

[38] - FAS population

[39] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: C-reactive Protein

End point title	Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: C-reactive Protein

End point description:

Biomarkers in blood that were analyzed included C-reactive protein (hCRP). hCRP is an acute phase reactant protein. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. CRP is an acute phase reactant protein

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[40]	47[41]		
Units: microgram per liter				
arithmetic mean (standard deviation)				
Baseline (N= 45, 45)	7.47 (± 7.325)	11.66 (± 14.582)		
Change at Day 14 (N= 42, 44)	-0.45 (± 4.584)	0.52 (± 8.834)		
Change at Day 28 (N= 44, 45)	2.9 (± 22.077)	2.46 (± 19.309)		
Change at Day 56 (N= 38, 42)	-0.62 (± 8.329)	4.96 (± 19.868)		

Notes:
[40] - FAS population
[41] - FAS population

Statistical analyses

Statistical analysis title	Biomarkers in Blood: Creactive Protein
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.927
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.539
upper limit	9.367

Secondary: Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Interleukin-8 (IL-8)

End point title	Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Interleukin-8 (IL-8)

End point description:

Biomarkers in blood that were analyzed included IL-8. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[42]	47[43]		
Units: nanogram per liter				
arithmetic mean (standard deviation)				
Baseline (N= 45, 45)	46.97 (± 185.099)	18.86 (± 12.88)		
Change at Day 14 (N= 42, 45)	14.8 (± 109.806)	10.34 (± 51.355)		
Change at Day 28 (N= 44, 45)	-29.85 (± 181.546)	7.68 (± 32.687)		
Change at Day 56 (N= 38, 43)	-35.19 (± 191.115)	3.42 (± 39.332)		

Notes:
[42] - FAS population
[43] - FAS population

Statistical analyses

Statistical analysis title	Biomarkers in Blood: Interleukin-8
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0771
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	-9.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.188
upper limit	1.063

Secondary: Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Neutrophil cell Count

End point title	Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Neutrophil cell Count

End point description:

Biomarkers in blood that were analyzed included neutrophil cell count. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[44]	47[45]		
Units: giga per liter				
arithmetic mean (standard deviation)				
Baseline (N= 45, 47)	4.331 (± 1.2776)	4.338 (± 1.4379)		
Change at Day 14 (N= 41, 45)	-0.056 (± 0.9886)	-0.257 (± 1.2292)		
Change at Day 28 (N= 44, 47)	0.122 (± 1.0209)	-0.2 (± 1.4049)		
Change at Day 56 (N= 39, 43)	-0.037 (± 0.9817)	0.377 (± 1.2587)		

Notes:
[44] - FAS population
[45] - FAS population

Statistical analyses

Statistical analysis title	Biomarkers in Blood: Neutrophil cell Count
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.143
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.643
upper limit	4.371

Secondary: Change From Baseline of Biomarkers in Urine At Days 14, 28, 56: Creatinine

End point title	Change From Baseline of Biomarkers in Urine At Days 14, 28, 56: Creatinine

End point description:

Biomarker assessments included creatinine in the urine. Concentrations of creatinine was measured and reported. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[46]	47[47]		
Units: micromole per liter				
arithmetic mean (standard deviation)				
Baseline (N= 42, 43)	7328.1 (± 5135.68)	7153.7 (± 4273.61)		
Change at Day 14 (N= 39, 41)	1598.1 (± 6149.83)	363.8 (± 2890.06)		
Change at Day 28 (N= 40, 39)	1221.8 (± 5070.3)	1856.5 (± 4082.98)		
Change at Day 56 (N= 37, 40)	1064.9 (± 6227.38)	948 (± 4387.41)		

Notes:
[46] - FAS population
[47] - FAS population

Statistical analyses

Statistical analysis title	Biomarkers in Urine: Creatinine
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5255
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	-585.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2413.24
upper limit	1242.474

Secondary: Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Desmosine

End point title	Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Desmosine

End point description:

Biomarker assessments included elastin degradation product desmosine in the urine. Desmosine was measured and reported. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[48]	47[49]		
Units: nanogram per milliliter				
arithmetic mean (standard deviation)				
Baseline (N= 42, 43)	10.816 (± 7.797)	12.812 (± 8.8276)		
Change at Day 14 (N= 39, 41)	2.262 (± 7.677)	0.371 (± 4.5118)		
Change at Day 28 (N= 40, 39)	2.744 (± 8.1192)	3.617 (± 5.9407)		
Change at Day 56 (N= 37, 40)	1.316 (± 9.6672)	1.577 (± 8.5245)		

Notes:
[48] - FAS population
[49] - FAS population

Statistical analyses

Statistical analysis title	Biomarkers in Urine: Desmosine
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3605
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	-1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.545
upper limit	1.673

Secondary: Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Normalized Desmosine Value to Creatinine

End point title	Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Normalized Desmosine Value to Creatinine

End point description:

Normalized desmosine value to creatinine is the ratio obtained by calculating assay of desmosine divided by assay of creatinine. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

End point values	BAY85-8501	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[50]	47[51]		
Units: nanogram per milligram				
arithmetic mean (standard deviation)				
Baseline (N= 42, 43)	13.926 (± 5.4532)	15.674 (± 4.2885)		
Change at Day 14 (N= 39, 41)	0.227 (± 4.227)	0.081 (± 3.4887)		
Change at Day 28 (N= 40, 39)	0.609 (± 3.6745)	0.651 (± 2.9772)		
Change at Day 56 (N= 37, 40)	0.096 (± 4.1133)	0.03 (± 4.4286)		

Notes:
[50] - FAS population
[51] - FAS population

Statistical analyses

Statistical analysis title	Normalized Desmosine Value to Creatinine
Comparison groups	BAY85-8501 v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7666
Method	ANCOVA
Parameter estimate	LS-mean Difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.756
upper limit	1.299

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment up to follow-up visit (28 days after last dose)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	BAY85-8501
Reporting group description:	
Daily oral dose of 1 mg BAY85-8501 tablets for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matched to BAY85-8501 for 28 days.	

Serious adverse events	BAY85-8501	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 45 (6.67%)	1 / 47 (2.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Accelerated idioventricular rhythm			
subjects affected / exposed	0 / 45 (0.00%)	1 / 47 (2.13%)	
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			
Apnoeic attack			
subjects affected / exposed	1 / 45 (2.22%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			

subjects affected / exposed	1 / 45 (2.22%)	0 / 47 (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 %

Non-serious adverse events	BAY85-8501	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 45 (40.00%)	20 / 47 (42.55%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 45 (11.11%)	4 / 47 (8.51%)	
occurrences (all)	9	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 45 (2.22%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	4 / 45 (8.89%)	3 / 47 (6.38%)	
occurrences (all)	6	4	
Vomiting			
subjects affected / exposed	3 / 45 (6.67%)	0 / 47 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 45 (8.89%)	4 / 47 (8.51%)	
occurrences (all)	5	4	
Sputum increased			
subjects affected / exposed	3 / 45 (6.67%)	3 / 47 (6.38%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 45 (6.67%)	0 / 47 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	2 / 45 (4.44%)	6 / 47 (12.77%)	
occurrences (all)	2	6	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 45 (6.67%)	1 / 47 (2.13%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2012	Measurement of the concentration of neutrophil elastase in the sputum was added as a biomarker endpoint. This endpoint allowed direct measurement of NE concentration (in sputum) as a biomarker endpoint; it was inadvertently omitted in the final stage of protocol preparation.

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes: