Clinical trial results:
Phase 3b Randomized, Double-Blind, Placebo-Controlled Two-Part Trial to Assess the Safety and Efficacy of Continuous Aztreonam for Inhalation Solution (AZLI) in Subjects With Cystic Fibrosis (CF) and Chronic Burkholderia Species Infection

Summary

EudraCT number	2009-011740-19
Trial protocol	Outside EU/EEA
Global end of trial date	12 September 2011

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	GS-US-205-0127

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01059565
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trial Mailbox , Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox , Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this research study was to determine if an experimental drug called Aztreonam for Inhalation Solution (AZLI) was safe and effective to treat Burkholderia lung infections in patients with cystic fibrosis (CF).

Spirometry was used to assess pulmonary function, and the revised Cystic Fibrosis Questionnaire (CFQ-R) was used to assess quality of life. The CFQ-R is a validated, patient-reported outcome tool used to measure health-related quality of life for children and adults with CF.

The study consisted of a 24-week randomized phase, and a 24-week open-label phase. Primary and secondary efficacy analyses were conducted for the 24-week randomized phase only. Safety data were collected for both the randomized and open-label phases.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2010
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: 94
Country: Number of subjects enrolled	Canada: 7
Worldwide total number of subjects	101
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)	4
Adolescents (12-17 years)	13
Adults (18-64 years)	84
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 34 sites in the United States and 1 site in Canada. The first participant was screened on 22 February 2010. The last participant observation was on 12 September 2011.

Pre-assignment

Screening details:

102 participants were screened and 101 were randomized. Of those participants randomized, 100 received at least one dose of study drug, and comprise the Safety Analysis Set and the Full Analysis Set.

Period 1

Period 1 title	24-Week Randomized Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	AZLI

Arm description:

Participants received Aztreonam for inhalation solution (AZLI) for 24 weeks during the randomized phase and continued to receive AZLI during the open-label phase.

Arm type	Experimental
Investigational medicinal product name	AZLI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Aztreonam for inhalation solution (AZLI; 75 mg aztreonam/52.5 mg lysine monohydrate) was administered three times a day, with at least 4 hours between doses, using the eFlow investigational nebulizer.

Arm title	Placebo

Arm description:

Participants received placebo to match AZLI for 24 weeks during the randomized phase and switched to AZLI during the open-label phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo to match AZLI (lactose and sodium chloride) was administered three times a day, with at least 4 hours between doses, using the eFlow investigational nebulizer.

Number of subjects in period 1[1]	AZLI	Placebo
Started	48	52
Randomized and treated	48	52
Completed	39	45
Not completed	9	7
Consent withdrawn by subject	3	1
Adverse event, non-fatal	5	-
Noncompliance with Study Drug Regimen	1	5
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant who was randomized but not treated in the study was not included in the subject disposition table.

Period 2

Period 2 title	24-Week Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AZLI/AZLI

Arm description:

Participants received Aztreonam for inhalation solution (AZLI) for 24 weeks during the randomized phase and continued to receive AZLI during the open-label phase.

Arm type	Experimental
Investigational medicinal product name	AZLI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Aztreonam for inhalation solution (AZLI; 75 mg aztreonam/52.5 mg lysine monohydrate) was administered three times a day, with at least 4 hours between doses, using the eFlow investigational nebulizer.

Arm title	Placebo/AZLI

Arm description:

Participants received placebo to match AZLI for 24 weeks during the randomized phase and switched to AZLI during the open-label phase.

Arm type	Placebo
Investigational medicinal product name	AZLI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Aztreonam for inhalation solution (AZLI; 75 mg aztreonam/52.5 mg lysine monohydrate) was

administered three times a day, with at least 4 hours between doses, using the eFlow investigational nebulizer.

Number of subjects in period 2	AZLI/AZLI	Placebo/AZLI
Started	39	45
Completed	34	42
Not completed	5	3
Subject noncompliance	1	-
Consent withdrawn by subject	1	-
Pulmonologist/participant decision	-	1
Adverse event, non-fatal	2	-
Worsening health (physician decision)	1	1
Unable to clean device (hospitalization)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AZLI
Reporting group description:	
Participants received Aztreonam for inhalation solution (AZLI) for 24 weeks during the randomized phase and continued to receive AZLI during the open-label phase.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to match AZLI for 24 weeks during the randomized phase and switched to AZLI during the open-label phase.	

Reporting group values	AZLI	Placebo	Total
Number of subjects	48	52	100
Age categorical Units: Subjects			
≥ 6 to ≤ 12 years	3	3	6
> 12 to < 18 years	3	8	11
≥ 18 years	42	41	83
Age Continuous Units: years			
arithmetic mean	28	24.7	
standard deviation	± 10.3	± 10	-
Gender, Male/Female Units: participants			
Female	22	17	39
Male	26	35	61
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	48	51	99
Unknown or Not Reported	0	0	0
Race Units: Subjects			
Black or African Heritage	1	2	3
White	46	50	96
Other	1	0	1
Forced expiratory volume in 1 second (FEV1) percent predicted			
FEV1 % predicted is defined as FEV1 % of the patient divided by the average FEV1 % in the population for any person of similar age, sex and body composition.			
Units: percentage of FEV1 % predicted			
arithmetic mean	60.67	52.59	
standard deviation	± 21.71	± 23.71	-
FEV1			
FEV1 is defined as the maximal volume of air that can be exhaled in 1 second.			
Units: liters			
arithmetic mean	2.13	1.93	
standard deviation	± 0.93	± 0.96	-
Forced vital capacity (FVC)			

FVC is defined as the volume of air that can forcibly be blown out after taking a full breath.			
Units: liters			
arithmetic mean	3.23	2.99	
standard deviation	± 1.18	± 1.14	-
Forced expiratory flow 25% to 75% (FEF25-75)			
FEF25-75 is defined as the forced expiratory flow from 25% to 75% of the FVC.			
Units: liters per second			
arithmetic mean	1.33	1.31	
standard deviation	± 0.95	± 1.22	-
Cystic Fibrosis Questionnaire - Revised (CFQ-R) Respiratory Symptoms Scale (RSS) Score			
Respiratory symptoms (e.g., coughing, congestion, wheezing) were assessed with the CFQ-R Respiratory Symptoms Scale (RSS). The range of scores (units) is 0 to 100 with higher scores indicating fewer symptoms.			
Units: units on a scale			
arithmetic mean	58.3	59	
standard deviation	± 21.4	± 17.6	-
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	21.9	20.7	
standard deviation	± 4.5	± 3.2	-
Burkholderia spp colony-forming units (CFU) in sputum			
Participants in the Full Analysis Set with evaluable assessments for Burkholderia spp. CFU in sputum at baseline were analyzed, which included 30 in the AZLI group, 32 in the placebo group, and 62 total.			
Units: log_10 CFU per gram			
arithmetic mean	6.39	6.41	
standard deviation	± 2.47	± 2.52	-

End points

End points reporting groups

Reporting group title	AZLI
Reporting group description:	
Participants received Aztreonam for inhalation solution (AZLI) for 24 weeks during the randomized phase and continued to receive AZLI during the open-label phase.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to match AZLI for 24 weeks during the randomized phase and switched to AZLI during the open-label phase.	
Reporting group title	AZLI/AZLI
Reporting group description:	
Participants received Aztreonam for inhalation solution (AZLI) for 24 weeks during the randomized phase and continued to receive AZLI during the open-label phase.	
Reporting group title	Placebo/AZLI
Reporting group description:	
Participants received placebo to match AZLI for 24 weeks during the randomized phase and switched to AZLI during the open-label phase.	

Primary: AUCave of relative change in FEV1 % predicted from baseline to Week 24

End point title	AUCave of relative change in FEV1 % predicted from baseline to Week 24
End point description:	
The relative change (AUCave) in FEV1 % predicted from baseline to Week 24 was analyzed. FEV1 % predicted is defined as FEV1 % of the patient divided by the average FEV1 % in the population for any person of similar age, sex and body composition. AUCave is the calculated area under the curve corrected for baseline and adjusted by the number of days on study through Week 24.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	52		
Units: percent change in FEV1% predicted				
least squares mean (standard error)	0.16 (± 1.5)	-0.75 (± 1.43)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Relative Change in FEV1 %
Statistical analysis description:	
The primary analysis was a test for superiority. Null hypothesis was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.	

A sample size of 50 participants per group provided at least 80% power to detect an 8.5% difference in mean AUCave of relative change from baseline in FEV1 % predicted through Week 24 using a two-sided 0.05-level test, assuming a common standard deviation of 15.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663 [1]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	5.06

Notes:

[1] - To correct for multiplicity, a family alpha spending rule was used to control the type 1 error rate of alpha = 0.05.

A gate-keeping procedure to control family-wise Type 1 error was established a priori for primary and key secondary endpoints.

Secondary: Total number of systemic and/or inhaled antibiotic courses for respiratory events

End point title	Total number of systemic and/or inhaled antibiotic courses for respiratory events

End point description:

The total number of systemic and/or inhaled antibiotic courses for respiratory events from baseline to Week 24 was analyzed. A single antibiotic course may represent the use of multiple antibiotics.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	52		
Units: antibiotic treatment courses				
number (not applicable)	54	73		

Statistical analyses

Statistical analysis title	AZLI vs placebo: # of Inhaled Antibiotic Courses

Statistical analysis description:

The primary analysis was a test for superiority. Null hypothesis was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4158 [2]
Method	Negative binomial regression

Notes:

[2] - To correct for multiplicity, a family alpha spending rule was used to control the type 1 error rate of alpha = 0.05.

The negative binomial regression model included an offset parameter to account for potential differing study durations.

Secondary: AUCave of change in CFQ-R RSS Scores from baseline to Week 24

End point title	AUCave of change in CFQ-R RSS Scores from baseline to Week 24

End point description:

The change (AUCave) in CFQ-R RSS scores from baseline to Week 24 was analyzed.

The range of scores (units) within the RSS domain is 0 to 100 with higher scores indicating fewer symptoms.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	52		
Units: units on a scale				
least squares mean (standard error)	2.97 (± 1.7)	2.79 (± 1.58)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Change in CFQ-R RSS Scores

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.939 [3]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	1.78

Notes:

[3] - To correct for multiplicity, a family alpha spending rule was used to control the type 1 error rate of alpha = 0.05.

The AUCs of changes from baseline were compared between treatment groups using ANCOVA methods with baseline value as a covariate.

Secondary: AUCave of relative change from baseline to Week 24 in FEV1

End point title	AUCave of relative change from baseline to Week 24 in FEV1

End point description:

The relative change (AUCave) from baseline to Week 24 in mean (SE) FEV1 was analyzed. FEV1 is defined as the maximal volume of air that can be exhaled in 1 second.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: percent change in FEV1 (liters)				
least squares mean (standard error)	0.36 (± 1.49)	-0.41 (± 1.42)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Relative change in FEV1

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.711 [4]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	4.86

Notes:

[4] - The AUCs of changes from baseline were compared between treatment groups using ANCOVA methods with baseline value as a covariate.

Secondary: AUCave of relative change from baseline to Week 24 in FVC

End point title	AUCave of relative change from baseline to Week 24 in FVC

End point description:

The relative change (AUCave) from baseline to Week 24 in mean (SE) FVC was analyzed. FVC is defined as the volume of air that can forcibly be blown out after taking a full breath.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: percent change in FVC (liters)				
least squares mean (standard error)	0.77 (± 1.42)	0.17 (± 1.35)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Relative Change in FVC

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.762 [5]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	4.49

Notes:

[5] - The AUCs of changes from baseline were compared between treatment groups using ANCOVA methods with baseline value as a covariate.

Secondary: AUCave of relative change from baseline to Week 24 in FEF25-75

End point title	AUCave of relative change from baseline to Week 24 in FEF25-75

End point description:

The relative change (AUCave) from baseline to Week 24 in mean (SE) FEF25-75 was analyzed. FEF25-75 is defined as the forced expiratory flow from 25% to 75% of the FVC.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: percent change in FEF25-75 (liters/sec)				
least squares mean (standard error)	1.4 (± 2.37)	-0.55 (± 2.25)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Relative Change in FEF25-75

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	Placebo v AZLI
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.553 [6]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.54
upper limit	8.44

Notes:

[6] - The AUCs of changes from baseline were compared between treatment groups using ANCOVA methods with baseline value as a covariate.

Secondary: AUCave of the change from baseline to Week 24 in physical functioning score as assessed by the CFQ-R

End point title	AUCave of the change from baseline to Week 24 in physical functioning score as assessed by the CFQ-R

End point description:

The change (AUCave) from baseline to Week 24 in the physical functioning score as assessed by the CFQ-R was analyzed.

The range of scores (units) in the CFQ-R physical functioning domain is 0 to 100 with higher scores indicating better QOL.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	52		
Units: units on a scale				
least squares mean (standard error)	1.06 (± 1.57)	-1.93 (± 1.48)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Physical Functioning Score

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17 [7]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	7.28

Notes:

[7] - Baseline was included as a covariate in this model.

Secondary: AUCave of the change from baseline to Week 24 in weight score as assessed by the CFQ-R

End point title	AUCave of the change from baseline to Week 24 in weight score as assessed by the CFQ-R

End point description:

The change (AUCave) from baseline to Week 24 in the weight score as assessed by the CFQ-R was analyzed.

The range of scores (units) in the CFQ-R weight domain is 0 to 100 with higher scores indicating better QOL.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	47		
Units: units on a scale				
least squares mean (standard error)	0.54 (± 2.9)	3.11 (± 2.8)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Change in Weight Score

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.528 [8]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	-2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.62
upper limit	5.49

Notes:

[8] - Baseline was included as a covariate in this model.

Secondary: AUCave of the change from baseline to Week 24 in treatment burden score as assessed by the CFQ-R

End point title	AUCave of the change from baseline to Week 24 in treatment burden score as assessed by the CFQ-R

End point description:

The change (AUCave) from baseline to Week 24 in the treatment burden score as assessed by the CFQ-R was analyzed.

The range of scores (units) in the CFQ-R treatment burden domain is 0 to 100 with higher scores indicating better QOL.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	52		
Units: units on a scale				
least squares mean (standard error)	-2.73 (± 1.73)	-6.35 (± 1.62)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Change in Treatment Burden Score

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.132 [9]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	3.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	8.34

Notes:

[9] - Baseline was included as a covariate in this model.

Secondary: Change in BMI from baseline to Week 24

End point title	Change in BMI from baseline to Week 24

End point description:

The change in BMI from baseline to Week 24 was analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: kg/m^2				
least squares mean (standard error)	0.34 (± 0.16)	0.21 (± 0.15)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Change in BMI

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.531 [10]
Method	Mixed models analysis
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.56

Notes:

[10] - P-value was based on a Mixed-Effect Model Repeated Measure model that included terms for treatment, visit, baseline, and treatment/visit interaction.

Secondary: Change in Burkholderia spp. CFU in sputum from baseline to Week 24

End point title	Change in Burkholderia spp. CFU in sputum from baseline to Week 24

End point description:

The change in Burkholderia spp. CFU in sputum from baseline to Week 24 was analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	20		
Units: log_10 CFU per gram of sputum				
least squares mean (standard error)	1.41 (± 0.58)	0.48 (± 0.5)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Change in Burkholderia Spp. CFU

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.232 [11]
Method	ANCOVA
Parameter estimate	Difference in least squares mean (LSM)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	2.48

Notes:

[11] - Baseline was included as a covariate in this model.

Secondary: Percentage of days participants used antibiotics

End point title	Percentage of days participants used antibiotics

End point description:

The percentage of days participants used antibiotics from baseline to Week 24 was analyzed. Antibiotics ongoing at baseline or started on or after first dose date were included in the analysis. A single antibiotic course could represent the use of multiple antibiotics. Days of antibiotic use included unique days.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: percentage of days				
arithmetic mean (standard deviation)	44.4 (± 35.2)	56.3 (± 34.8)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Percent of Days Using Antibiotics

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.103
Method	Wilcoxon (Mann-Whitney)

Secondary: Percent of days hospitalized

End point title	Percent of days hospitalized

End point description:

The percentage of days hospitalized from baseline to Week 24 was analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	52		
Units: percentage of days				
arithmetic mean (standard deviation)	4.9 (± 10.3)	4.8 (± 8.7)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Percent of Days Hospitalized

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.646
Method	Wilcoxon (Mann-Whitney)

Secondary: Percentage of missed school or work days

End point title	Percentage of missed school or work days

End point description:

The percentage of days participants missed school or work from baseline to Week 24 was analyzed.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	40		
Units: percentage of days				
arithmetic mean (standard deviation)	1.9 (± 3.3)	4.7 (± 7.2)		

Statistical analyses

Statistical analysis title	AZLI vs placebo: Percent Missed School/Work Days

Statistical analysis description:

Null hypothesis was that there was no difference between the AZLI and placebo treatment groups versus the alternative hypothesis that there was a difference.

Comparison groups	AZLI v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.284
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Week 24	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	AZLI
Reporting group description:	
For the reporting of Adverse Events, this group includes participants who were randomized to receive AZLI at baseline, and were analyzed from Baseline to Week 24.	
Reporting group title	Placebo
Reporting group description:	
For the reporting of Adverse Events, this group includes participants who were randomized to receive placebo at baseline, and were analyzed from Baseline to Week 24.	
Reporting group title	Open-Label AZLI
Reporting group description:	
For the reporting of Adverse Events, this group includes participants who were randomized to receive either AZLI or placebo at baseline and switched to open-label AZLI for up to 24 weeks (analyzed from Week 24 to Week 48).	

Serious adverse events	AZLI	Placebo	Open-Label AZLI
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 48 (35.42%)	21 / 52 (40.38%)	43 / 84 (51.19%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	0	0	0
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Procedural site reaction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Haematospermia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 48 (2.08%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 52 (0.00%)	4 / 84 (4.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus disorder			
subjects affected / exposed	1 / 48 (2.08%)	0 / 52 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 48 (2.08%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 48 (2.08%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lung disorder			

subjects affected / exposed	7 / 48 (14.58%)	14 / 52 (26.92%)	18 / 84 (21.43%)
occurrences causally related to treatment / all	0 / 11	0 / 20	0 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory arrest			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholethiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 48 (2.08%)	0 / 52 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthritis reactive			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cycstic fibrosis			
subjects affected / exposed	10 / 48 (20.83%)	6 / 52 (11.54%)	19 / 84 (22.62%)
occurrences causally related to treatment / all	0 / 10	0 / 10	0 / 26
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 52 (1.92%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AZLI	Placebo	Open-Label AZLI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)	46 / 52 (88.46%)	83 / 84 (98.81%)
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	2 / 48 (4.17%)	3 / 52 (5.77%)	6 / 84 (7.14%)
occurrences (all)	2	4	7
Pulmonary function test decreased			
subjects affected / exposed	5 / 48 (10.42%)	8 / 52 (15.38%)	12 / 84 (14.29%)
occurrences (all)	5	8	17
Weight decreased			

subjects affected / exposed	3 / 48 (6.25%)	3 / 52 (5.77%)	11 / 84 (13.10%)
occurrences (all)	3	5	13
Breath sounds abmormal			
subjects affected / exposed	2 / 48 (4.17%)	0 / 52 (0.00%)	6 / 84 (7.14%)
occurrences (all)	2	0	7
Vitamin D decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 52 (0.00%)	6 / 84 (7.14%)
occurrences (all)	0	0	6
Oxygen saturation decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	5 / 84 (5.95%)
occurrences (all)	0	1	6
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 52 (3.85%)	6 / 84 (7.14%)
occurrences (all)	0	2	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 48 (10.42%)	3 / 52 (5.77%)	1 / 84 (1.19%)
occurrences (all)	6	4	1
Headache			
subjects affected / exposed	6 / 48 (12.50%)	7 / 52 (13.46%)	14 / 84 (16.67%)
occurrences (all)	6	9	21
Sinus headache			
subjects affected / exposed	8 / 48 (16.67%)	3 / 52 (5.77%)	10 / 84 (11.90%)
occurrences (all)	8	4	11
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	13 / 48 (27.08%)	8 / 52 (15.38%)	15 / 84 (17.86%)
occurrences (all)	15	9	23
Chest pain			
subjects affected / exposed	7 / 48 (14.58%)	1 / 52 (1.92%)	23 / 84 (27.38%)
occurrences (all)	7	1	28
Chills			
subjects affected / exposed	6 / 48 (12.50%)	2 / 52 (3.85%)	11 / 84 (13.10%)
occurrences (all)	6	2	12
Exercise tolerance decreased			

subjects affected / exposed	5 / 48 (10.42%)	1 / 52 (1.92%)	4 / 84 (4.76%)
occurrences (all)	5	1	4
Fatigue			
subjects affected / exposed	10 / 48 (20.83%)	11 / 52 (21.15%)	26 / 84 (30.95%)
occurrences (all)	11	14	30
Non-cardiac chest pain			
subjects affected / exposed	3 / 48 (6.25%)	3 / 52 (5.77%)	5 / 84 (5.95%)
occurrences (all)	3	3	6
Pain			
subjects affected / exposed	6 / 48 (12.50%)	2 / 52 (3.85%)	8 / 84 (9.52%)
occurrences (all)	7	2	10
Pyrexia			
subjects affected / exposed	19 / 48 (39.58%)	17 / 52 (32.69%)	35 / 84 (41.67%)
occurrences (all)	28	24	52
Asthenia			
subjects affected / exposed	4 / 48 (8.33%)	3 / 52 (5.77%)	6 / 84 (7.14%)
occurrences (all)	5	3	6
Malaise			
subjects affected / exposed	1 / 48 (2.08%)	1 / 52 (1.92%)	5 / 84 (5.95%)
occurrences (all)	1	1	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 48 (6.25%)	3 / 52 (5.77%)	10 / 84 (11.90%)
occurrences (all)	5	3	12
Abdominal pain upper			
subjects affected / exposed	4 / 48 (8.33%)	1 / 52 (1.92%)	3 / 84 (3.57%)
occurrences (all)	4	1	3
Constipation			
subjects affected / exposed	3 / 48 (6.25%)	3 / 52 (5.77%)	6 / 84 (7.14%)
occurrences (all)	4	3	8
Diarrhoea			
subjects affected / exposed	6 / 48 (12.50%)	6 / 52 (11.54%)	10 / 84 (11.90%)
occurrences (all)	6	8	11
Nausea			
subjects affected / exposed	11 / 48 (22.92%)	10 / 52 (19.23%)	14 / 84 (16.67%)
occurrences (all)	13	11	15

Vomiting			
subjects affected / exposed	7 / 48 (14.58%)	5 / 52 (9.62%)	8 / 84 (9.52%)
occurrences (all)	7	5	10
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 48 (70.83%)	32 / 52 (61.54%)	65 / 84 (77.38%)
occurrences (all)	52	59	129
Dyspnoea			
subjects affected / exposed	14 / 48 (29.17%)	15 / 52 (28.85%)	38 / 84 (45.24%)
occurrences (all)	20	21	57
Haemoptysis			
subjects affected / exposed	13 / 48 (27.08%)	17 / 52 (32.69%)	19 / 84 (22.62%)
occurrences (all)	25	22	33
Increased viscosity of bronchial secretion			
subjects affected / exposed	4 / 48 (8.33%)	2 / 52 (3.85%)	3 / 84 (3.57%)
occurrences (all)	5	2	3
Nasal congestion			
subjects affected / exposed	12 / 48 (25.00%)	14 / 52 (26.92%)	30 / 84 (35.71%)
occurrences (all)	14	15	34
Oropharyngeal pain			
subjects affected / exposed	15 / 48 (31.25%)	11 / 52 (21.15%)	30 / 84 (35.71%)
occurrences (all)	17	13	33
Paranasal sinus hypersecretion			
subjects affected / exposed	2 / 48 (4.17%)	3 / 52 (5.77%)	4 / 84 (4.76%)
occurrences (all)	2	4	4
Pleuritic pain			
subjects affected / exposed	3 / 48 (6.25%)	0 / 52 (0.00%)	4 / 84 (4.76%)
occurrences (all)	4	0	5
Productive cough			
subjects affected / exposed	4 / 48 (8.33%)	1 / 52 (1.92%)	8 / 84 (9.52%)
occurrences (all)	8	2	12
Rales			
subjects affected / exposed	5 / 48 (10.42%)	6 / 52 (11.54%)	13 / 84 (15.48%)
occurrences (all)	6	8	15
Respiratory tract congestion			

subjects affected / exposed	7 / 48 (14.58%)	14 / 52 (26.92%)	24 / 84 (28.57%)
occurrences (all)	9	17	28
Rhinorrheoa			
subjects affected / exposed	8 / 48 (16.67%)	6 / 52 (11.54%)	19 / 84 (22.62%)
occurrences (all)	9	6	22
Sinus congestion			
subjects affected / exposed	8 / 48 (16.67%)	5 / 52 (9.62%)	15 / 84 (17.86%)
occurrences (all)	11	5	19
Sputum discoloured			
subjects affected / exposed	1 / 48 (2.08%)	3 / 52 (5.77%)	8 / 84 (9.52%)
occurrences (all)	1	3	11
Sputum increased			
subjects affected / exposed	23 / 48 (47.92%)	20 / 52 (38.46%)	33 / 84 (39.29%)
occurrences (all)	31	28	47
Upper-airway cough syndrome			
subjects affected / exposed	4 / 48 (8.33%)	6 / 52 (11.54%)	4 / 84 (4.76%)
occurrences (all)	4	6	4
Wheezing			
subjects affected / exposed	10 / 48 (20.83%)	3 / 52 (5.77%)	14 / 84 (16.67%)
occurrences (all)	11	4	20
Epistaxis			
subjects affected / exposed	2 / 48 (4.17%)	2 / 52 (3.85%)	5 / 84 (5.95%)
occurrences (all)	2	2	6
Pharyngeal erythema			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	5 / 84 (5.95%)
occurrences (all)	0	1	5
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 48 (6.25%)	0 / 52 (0.00%)	2 / 84 (2.38%)
occurrences (all)	3	0	2
Pruritus			
subjects affected / exposed	1 / 48 (2.08%)	3 / 52 (5.77%)	3 / 84 (3.57%)
occurrences (all)	1	3	4
Rash			
subjects affected / exposed	2 / 48 (4.17%)	1 / 52 (1.92%)	8 / 84 (9.52%)
occurrences (all)	2	1	9

Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 48 (8.33%)	1 / 52 (1.92%)	9 / 84 (10.71%)
occurrences (all)	4	1	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 48 (6.25%)	6 / 52 (11.54%)	8 / 84 (9.52%)
occurrences (all)	4	7	8
Back pain			
subjects affected / exposed	4 / 48 (8.33%)	6 / 52 (11.54%)	6 / 84 (7.14%)
occurrences (all)	5	6	6
Pain in extremity			
subjects affected / exposed	1 / 48 (2.08%)	2 / 52 (3.85%)	5 / 84 (5.95%)
occurrences (all)	1	3	5
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 52 (1.92%)	6 / 84 (7.14%)
occurrences (all)	0	1	6
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 48 (0.00%)	3 / 52 (5.77%)	1 / 84 (1.19%)
occurrences (all)	0	3	1
Sinusitis			
subjects affected / exposed	1 / 48 (2.08%)	4 / 52 (7.69%)	9 / 84 (10.71%)
occurrences (all)	1	4	10
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 48 (16.67%)	6 / 52 (11.54%)	15 / 84 (17.86%)
occurrences (all)	9	7	18
Hyperglycaemia			
subjects affected / exposed	3 / 48 (6.25%)	0 / 52 (0.00%)	2 / 84 (2.38%)
occurrences (all)	3	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2009	Added an optional screening period and references to "Visit 1" and "Visit 2" were changed to "Screening" or "Baseline" for clarity because some subjects might have a combination visit instead.
18 May 2010	Clarified the definition of chronic infection with Burkholderia spp. to include bronchoalveolar lavage and oropharyngeal swab cultures in addition to sputum cultures.
12 July 2010	To increase the sample size from 76 subjects to 100 subjects.

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.

There were no limitations affecting the analysis or results.

Notes: