Clinical trial results:
A Double-Blind, Multicenter, Multinational, Randomized, Placebo-Controlled Trial Evaluating Aztreonam Lysine For Inhalation in Patients With Cystic Fibrosis, Mild Lung Disease, and P. Aeruginosa (AIR-CF4)

Summary

EudraCT number	2015-000395-97
Trial protocol	Outside EU/EEA
Global end of trial date	19 June 2009

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-205-0117

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00712166
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences, Inc.
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	19 June 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of a 28-day course of aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis (CF), mild lung disease (forced expiratory volume in 1 second [FEV1] >75% predicted), and Pseudomonas aeruginosa (PA) infection.

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	16 June 2008
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	Canada: 2
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	United States: 145
Worldwide total number of subjects	157
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)	22
Adolescents (12-17 years)	67
Adults (18-64 years)	68
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 39 sites in total: 34 in the United States, 1 in Canada, and 4 in Australia. Date of first screening was 16 June 2008, and date of last participant observation was 19 June 2009.

Pre-assignment

Screening details:

Planned trial size was approximately 140 participants randomized in 1:1 ratio to aztreonam for inhalation solution (AZLI) three times daily (TID) or placebo TID. 160 participants were randomized, 157 received blinded study drug (76 AZLI; 81 placebo). One participant who was randomized and treated with study drug discontinued the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo to match AZLI self administered 3 times daily (TID) for the duration of the study.

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

Dosage and administration details:

Placebo to match AZLI (5 mg/mL lactose when reconstituted in diluent [0.17% saline]; sterile, pH 4.2 to 7.5, and osmolality 200 to 400 mOsmol/kg) administered using an eFlow nebulizer

Arm title	AZLI

Arm description:

Participants received AZLI self administered 3 times daily for the duration of the study.

Arm type	Experimental
Investigational medicinal product name	Aztreonam for inhalation solution
Investigational medicinal product code	
Other name	AZLI, Cayston®
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

AZLI (75 mg aztreonam and 52.5 mg lysine monohydrate reconstituted in diluent [0.17% saline] with a pH of 4.4 to 5.4, and osmolality 350 to 550 mOsmol/kg) administered using an eFlow nebulizer

Number of subjects in period 1	Placebo	AZLI
Started	81	76
Completed	81	75
Not completed	0	1
Noncompliance	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo to match AZLI self administered 3 times daily (TID) for the duration of the study.	
Reporting group title	AZLI
Reporting group description:	
Participants received AZLI self administered 3 times daily for the duration of the study.	

Reporting group values	Placebo	AZLI	Total
Number of subjects	81	76	157
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	18.9	19.5	
standard deviation	± 9.11	± 9.07	-
Gender categorical			
Units: Subjects			
Female	37	30	67
Male	44	46	90

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo to match AZLI self administered 3 times daily (TID) for the duration of the study.	
Reporting group title	AZLI
Reporting group description:	
Participants received AZLI self administered 3 times daily for the duration of the study.	

Primary: Change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory symptoms scale (RSS) score at Day 28

End point title	Change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory symptoms scale (RSS) score at Day 28
End point description:	
The CFQ-R is a validated patient-reported outcome measuring health-related quality of life for children and adults with CF. The CFQ-R contains both general and CF-specific scales. The CFQ-R was administered at Days 0, 14, 28, and 42. The endpoint was change in respiratory symptoms (e.g., coughing, congestion, wheezing) from Day 0 (baseline), assessed with the CFQ-R RSS (score range: 0-100; higher scores indicating fewer symptoms, higher health-related quality of life, or better functioning). Baseline CFQ-R RSS and age group (<18 vs. >=18 years) were included as covariates in the analysis. Analysis on intent-to-treat (ITT) population (received at least part of 1 dose of AZLI/placebo). Missing baseline data not imputed. Missing post-baseline data imputed with worst-case value for participants who withdrew due to an adverse event (AE)/study drug intolerance. Imputation for other missing data was last observation carried forward (LOCF).	
End point type	Primary
End point timeframe:	
Day 0 to Day 28	

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	75		
Units: Units on a scale				
least squares mean (standard error)	1.41 (± 1.64)	3.22 (± 1.71)		

Statistical analyses

Statistical analysis title	Difference in change from baseline
Statistical analysis description:	
Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in change from baseline in CFQ-R RSS score at Day 28. At the 5% significance level (i.e., α = 0.05) using a two-sided significance test, a sample size of 70 participants per treatment group provided at least 90% power to detect a 10 point difference between groups in the mean change from baseline at Day 28 in the CFQ-R RSS score, assuming a common standard deviation (SD) of 17.5.	
Comparison groups	Placebo v AZLI

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.433 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.83
upper limit	6.44

Notes:

[1] - The primary endpoint analysis was based on a two-sided test with an 0.05 a priori threshold for statistical significance. A gate-keeper approach was established a priori to control the type 1 error rate, however, the primary endpoint was not met.

Secondary: Change from baseline in CFQ-R RSS score at Day 14

End point title	Change from baseline in CFQ-R RSS score at Day 14

End point description:

The CFQ-R is a validated patient-reported outcome measuring health-related quality of life for children and adults with CF. The CFQ-R contains both general and CF-specific scales. The CFQ-R was administered at Days 0, 14, 28, and 42. The endpoint was change in respiratory symptoms (e.g., coughing, congestion, wheezing) from Day 0 (baseline), assessed with the CFQ-R RSS (score range: 0-100; higher scores indicating fewer symptoms, higher health-related quality of life, or better functioning). Baseline CFQ-R RSS and age group (<18 vs. >=18 years) were included as covariates in the analysis. Analysis based on ITT population (all participants receiving at least part of one dose of AZLI or placebo). Missing baseline data were not imputed. Missing post-baseline data were imputed using worst-case value for participants who withdrew due to an AE or study drug intolerance. For all other missing data, LOCF imputation method was used.

End point type	Secondary

End point timeframe:

Day 0 to Day 14

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	75		
Units: Units on a scale				
least squares mean (standard error)	0.28 (± 1.56)	3.65 (± 1.63)		

Statistical analyses

Statistical analysis title	Difference in change from baseline

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in change from baseline in the CFQ-R RSS score at Day 14.

Comparison groups	Placebo v AZLI

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.133 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	7.78

Notes:

[2] - Intergroup analysis of change from baseline in RSS score.

[3] - No adjustments were made for multiple comparisons.

Secondary: Change from baseline in CFQ-R RSS score at Day 42

End point title	Change from baseline in CFQ-R RSS score at Day 42

End point description:

The CFQ-R is a validated patient-reported outcome measuring health-related quality of life for children and adults with CF. The CFQ-R contains both general and CF-specific scales. The CFQ-R was administered at Days 0, 14, 28, and 42. The endpoint was change in respiratory symptoms (e.g., coughing, congestion, wheezing) from Day 0 (baseline), assessed with the CFQ-R RSS (score range: 0-100; higher scores indicating fewer symptoms, higher health-related quality of life, or better functioning). Baseline CFQ-R RSS and age group (<18 vs. >=18 years) were included as covariates in the analysis. Analysis based on ITT population (all participants receiving at least part of one dose of AZLI or placebo). Missing baseline data were not imputed. Missing post-baseline data were imputed using worst-case value for participants who withdrew due to an AE or study drug intolerance. For all other missing data, LOCF imputation method was used.

End point type	Secondary

End point timeframe:

Day 0 to Day 42

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	75		
Units: Units on a scale				
least squares mean (standard error)	2.91 (± 1.65)	3.02 (± 1.72)		

Statistical analyses

Statistical analysis title	Difference in change from baseline

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in change from baseline in the CFQ-R RSS score at Day 42.

Comparison groups	Placebo v AZLI

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.965 [5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.56
upper limit	4.76

Notes:

[4] - Intergroup analysis of change from baseline in RSS score.

[5] - No adjustments were made for multiple comparisons.

Secondary: Change From Baseline in CFQ-R Physical Functioning Domain Score

End point title	Change From Baseline in CFQ-R Physical Functioning Domain Score

End point description:

The CFQ-R contains both general and CF-specific scales. The CFQ-R was administered at Days 0 (baseline), 14,
28, and 42 (the last study visit). The endpoint was change from baseline in the physical functioning domain (e.g., ability to walk and engage in physical activities) of the CFQ-R at Day 28 (range of scores: 0-100; higher scores indicating fewer symptoms, higher health-related quality of life, or better functioning). Baseline CFQ-R physical functioning domain score and age group (<18 vs. >=18 years) were included as covariates in the analysis. Analysis based on ITT population (all participants receiving at least part of one dose of AZLI or placebo). Missing baseline data were not imputed. Missing post-baseline data were imputed using worst-case value for participants who withdrew due to an AE or study drug intolerance. For all other missing data, LOCF imputation method was used.

End point type	Secondary

End point timeframe:

Day 0 to Day 28

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	76		
Units: Units on a scale				
least squares mean (standard error)	-0.69 (± 1.53)	1.79 (± 1.57)		

Statistical analyses

Statistical analysis title	Difference in change from baseline

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in change from baseline in the CFQ-R physical functioning domain score at Day 28.

Comparison groups	Placebo v AZLI

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.256 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	6.76

Notes:

[6] - Intergroup analysis of change from baseline in physical domain score.

[7] - No adjustments were made for multiple comparisons.

Secondary: Number of participants using additional (nonprotocol-specified) antipseudomonal antibiotics during study

End point title	Number of participants using additional (nonprotocol-specified) antipseudomonal antibiotics during study

End point description:

The number of participants requiring additional antipseudomonal antibiotics (oral, intravenous [IV], or by inhalation), the time to use of these antibiotics, and the reasons for use was recorded. A binary variable was defined to indicate whether the participants needed any antipseudomonal antibiotics that were non-study drug via the oral, IV, or inhalation route between Day 0 (Baseline Visit) and Day 42 (Visit 5). Fisher's Exact Test was implemented on the intent-to-treat (ITT) and per protocol analysis sets to detect treatment effects on need for additional antipseudomonal antibiotics. Analysis based on ITT population (all participants who received at least part of one dose of AZLI or placebo). No imputation methods were used for the analysis.

End point type	Secondary

End point timeframe:

Day 0 to Day 42

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	76		
Units: Participants	21	19		

Statistical analyses

Statistical analysis title	Difference in antibiotic use

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in number of participants using additional (nonprotocol-specified) antipseudomonal antibiotics during study.

Comparison groups	Placebo v AZLI

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	> 0.999 [9]
Method	Fisher exact

Notes:

[8] - Intergroup analysis of nonprotocol-specified antipseudomonal antibiotic use.

[9] - No adjustments were made for multiple comparisons.

Secondary: Number of participants hospitalized during study

End point title	Number of participants hospitalized during study

End point description:

Hospitalization was defined as any hospital admission lasting for more than 1 calendar day that had been recorded as a serious adverse event (SAE) on the electronic case report form (eCRF). Binary variables were defined to indicate whether participants experienced any hospitalization. Number of hospitalizations was summarized by treatment group. Analysis based on ITT population (all participants who received at least part of one dose of AZLI or placebo). No imputation methods were used for the analysis.

End point type	Secondary

End point timeframe:

Day 0 to Day 42

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	76		
Units: Participants	3	8		

Statistical analyses

Statistical analysis title	Difference in hospitalization rate

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in proportion of participants hospitalized.

Comparison groups	Placebo v AZLI
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.122 [11]
Method	Fisher exact

Notes:

[10] - Intergroup analysis of hospitalization rate.

[11] - No adjustments were made for multiple comparisons.

Secondary: Change from baseline in Log10 Pseudomonas aeruginosa (PA) colony forming units (CFUs) in sputum at Day 28

End point title	Change from baseline in Log10 Pseudomonas aeruginosa (PA) colony forming units (CFUs) in sputum at Day 28

End point description:

Sputum samples were collected at all study visits for quantitative and qualitative culture for PA. Sputum PA density was quantified by logarithm transformation of the CFU value with base 10. Change from baseline in sputum PA density was calculated as the difference between the log10 CFU values at Day 28 (Visit 4) and the baseline value. Missing data was not imputed. Baseline log10 CFU and age group (<18 vs. >=18 years) were included as covariates in the analysis. Analysis based on ITT population (all participants who received at least part of one dose of AZLI or placebo). No imputation methods were used for the analysis.

End point type	Secondary

End point timeframe:

Day 0 to Day 28

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	37		
Units: Log10 PA CFUs/gram of sputum				
least squares mean (standard error)	-0.14 (± 0.36)	-1.35 (± 0.36)		

Statistical analyses

Statistical analysis title	Difference in change from baseline

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in change from baseline in the log10 CFU at Day 28.

Comparison groups	Placebo v AZLI
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.016 [13]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-0.23

Notes:

[12] - Intergroup analysis of change from baseline.

[13] - No adjustments were made for multiple comparisons.

Secondary: Relative change from baseline in forced expiratory volume in 1 second (FEV1) percent predicted

End point title	Relative change from baseline in forced expiratory volume in 1 second (FEV1) percent predicted

End point description:

Spirometry was performed according to American Thoracic Society (ATS) guidelines at each visit. Treatment effect on the relative change from baseline in FEV1 percent predicted at Day 28 (Visit 4) was tested by the ANCOVA model using the ITT analysis set. Baseline FEV1 percent predicted and age group (<18 vs. >=18 years) were included as covariates in the analysis. Analysis based on ITT population (all

participants who received at least part of one dose of AZLI or placebo). Missing baseline data were not imputed. Missing postbaseline data were imputed using worst-case value for participants who withdrew due to an AE or study drug intolerance. For all other missing data, LOCF method was used.

End point type	Secondary

End point timeframe:

Day 0 to Day 28

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	76		
Units: Percent change from baseline				
least squares mean (standard error)	-2.45 (± 0.82)	0.29 (± 0.85)		

Statistical analyses

Statistical analysis title	Difference in relative change from baseline

Statistical analysis description:

Null hypothesis was there was no difference between 75 mg AZLI TID and placebo treatment groups in % change from baseline in FEV1 % predicted at Day 28.

Comparison groups	Placebo v AZLI
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.021 [15]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	5.04

Notes:

[14] - Intergroup analysis of relative change from baseline.

[15] - No adjustments were made for multiple comparisons.

Secondary: Number of participants testing positive for other respiratory pathogens

End point title	Number of participants testing positive for other respiratory pathogens

End point description:

Sputum/throat swab samples were collected at all visits for quantitative and qualitative culture of Burkholderia species, Stenotrophomonas maltophilia, Achromobacter xylosidans, methicillin-resistant Staphylococcus aureus (MRSA), methicillin-sensitive S. aureus (MSSA), and Aspergillus species. One CFU on the culture from either a sputum or throat swab sample was considered presence of the particular organism. Analysis based on ITT population (all participants who received at least part of one dose of AZLI or placebo). No imputation methods were used for the analysis.

End point type	Secondary

End point timeframe:

Day 0 to Day 28

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	76		
Units: Participants				
B. cepacia - Day 0	1	0		
B. cepacia - Day 28	1	1		
S. maltophilia - Day 0	7	8		
S. maltophilia - Day 28	9	8		
A. xylosoxidans - Day 0	0	1		
A. xylosoxidans - Day 28	2	1		
MRSA - Day 0	14	14		
MRSA - Day 28	13	13		
MSSA - Day 0	31	28		
MSSA - Day 28	31	25		
Aspergillus spp. - Day 0	6	10		
Aspergillus spp. - Day 28	6	11		

Statistical analyses

No statistical analyses for this end point

Secondary: The Minimum Concentrations of Aztreonam that Inhibit 50% and 90% of all PA Isolates (MIC50 and MIC90, respectively)

End point title	The Minimum Concentrations of Aztreonam that Inhibit 50% and 90% of all PA Isolates (MIC50 and MIC90, respectively)

End point description:

Aztreonam susceptibility of PA isolates from expectorated sputum samples (collected at all visits) was assessed. The minimum inhibitory concentration (MIC) is the lowest concentration of antimicrobial agent that inhibits visible growth of a microorganism. The MIC50 and MIC90 for PA is the MIC required to inhibit the growth of 50% or 90% of PA isolates, respectively. Given that there might be multiple PA isolates for each participant, the MIC50 and MIC90 for PA was calculated using the MIC values for all PA isolates. The MIC50 and MIC90 were calculated by treatment group. Analysis based on ITT population (all participants who received at least part of one dose of AZLI or placebo).

Baseline and Day 28 MIC50 were ≤ 1 in the Placebo Group, and baseline MIC50 was ≤ 1 in the AZLI Group.

End point type	Secondary

End point timeframe:

Day 0 to Day 28

End point values	Placebo	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	76		
Units: µg/mL				
Baseline MIC50	1	1		
Day 28 MIC50	1	4		
Baseline MIC90	16	8		
Day 28 MIC90	16	32		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs were collected continuously from the first dose (Day 0) until 14 days after last AZLI/placebo dose (typically Day 42). Participants who discontinued were evaluated for at least 14 days after last dose of study drug.

Adverse event reporting additional description:

An AE was any physical/clinical worsening in symptoms/disease (including clinically significant change in lab values) experienced by participant at any time during study, whether or not event was considered related to study participation or study procedures. Participants were only counted once within a System Organ Class (SOC) and preferred term.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo to match AZLI self administered 3 times daily (TID) for the duration of the study.

Reporting group title	AZLI

Reporting group description:

Participants received AZLI self administered 3 times daily for the duration of the study.

Serious adverse events	Placebo	AZLI	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 81 (3.70%)	9 / 76 (11.84%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	1 / 81 (1.23%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breath sounds abnormal			
subjects affected / exposed	0 / 81 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	2 / 81 (2.47%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 81 (1.23%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 81 (1.23%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 81 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 81 (1.23%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 81 (1.23%)	3 / 76 (3.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 81 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 76 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 81 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	AZLI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 81 (71.60%)	53 / 76 (69.74%)	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	8 / 81 (9.88%)	6 / 76 (7.89%)	
occurrences (all)	8	6	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 81 (12.35%)	14 / 76 (18.42%)	
occurrences (all)	12	17	
Sinus headache			
subjects affected / exposed	3 / 81 (3.70%)	5 / 76 (6.58%)	
occurrences (all)	4	8	
Dizziness			

subjects affected / exposed	1 / 81 (1.23%)	5 / 76 (6.58%)	
occurrences (all)	2	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 81 (12.35%)	6 / 76 (7.89%)	
occurrences (all)	11	7	
Pyrexia			
subjects affected / exposed	7 / 81 (8.64%)	5 / 76 (6.58%)	
occurrences (all)	8	6	
Chest pain			
subjects affected / exposed	2 / 81 (2.47%)	4 / 76 (5.26%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 81 (11.11%)	3 / 76 (3.95%)	
occurrences (all)	9	3	
Abdominal pain			
subjects affected / exposed	9 / 81 (11.11%)	1 / 76 (1.32%)	
occurrences (all)	9	1	
Abdominal pain upper			
subjects affected / exposed	3 / 81 (3.70%)	5 / 76 (6.58%)	
occurrences (all)	5	6	
Nausea			
subjects affected / exposed	6 / 81 (7.41%)	2 / 76 (2.63%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 81 (37.04%)	32 / 76 (42.11%)	
occurrences (all)	32	35	
Productive cough			
subjects affected / exposed	13 / 81 (16.05%)	18 / 76 (23.68%)	
occurrences (all)	13	18	
Nasal congestion			
subjects affected / exposed	15 / 81 (18.52%)	13 / 76 (17.11%)	
occurrences (all)	15	13	
Oropharyngeal pain			

subjects affected / exposed	11 / 81 (13.58%)	12 / 76 (15.79%)	
occurrences (all)	12	12	
Rhinorrhoea			
subjects affected / exposed	12 / 81 (14.81%)	8 / 76 (10.53%)	
occurrences (all)	12	10	
Respiratory tract congestion			
subjects affected / exposed	6 / 81 (7.41%)	11 / 76 (14.47%)	
occurrences (all)	6	11	
Rales			
subjects affected / exposed	5 / 81 (6.17%)	7 / 76 (9.21%)	
occurrences (all)	5	7	
Dyspnoea			
subjects affected / exposed	4 / 81 (4.94%)	7 / 76 (9.21%)	
occurrences (all)	5	7	
Postnasal drip			
subjects affected / exposed	7 / 81 (8.64%)	3 / 76 (3.95%)	
occurrences (all)	7	3	
Wheezing			
subjects affected / exposed	5 / 81 (6.17%)	5 / 76 (6.58%)	
occurrences (all)	5	5	
Chest discomfort			
subjects affected / exposed	2 / 81 (2.47%)	6 / 76 (7.89%)	
occurrences (all)	2	6	
Sputum discoloured			
subjects affected / exposed	5 / 81 (6.17%)	3 / 76 (3.95%)	
occurrences (all)	5	4	
Pleuritic pain			
subjects affected / exposed	0 / 81 (0.00%)	4 / 76 (5.26%)	
occurrences (all)	0	4	
Infections and infestations			
Rhinitis			
subjects affected / exposed	4 / 81 (4.94%)	5 / 76 (6.58%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	6 / 76 (7.89%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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: