Clinical trial results:
An Open-Label, Randomized, Phase 3 Trial to Evaluate the Efficacy and Safety of Aztreonam 75 mg Powder and Diluent for Nebuliser Solution (AZLI) versus Tobramycin Nebuliser Solution (TNS) in an Intermittent Aerosolized Antibiotic Regimen, in Subjects with Cystic Fibrosis Followed by an Open-Label, Single Arm Extension

Summary

EudraCT number	2007-004277-26
Trial protocol	BE FR ES GB IE DK DE NL IT PT AT Outside EU/EEA
Global end of trial date	22 November 2010

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-205-0110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00757237
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000827-PIP01-09
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	17 May 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the comparative safety and effectiveness of aztreonam 75 mg powder and diluent for nebuliser solution (AZLI) versus tobramycin nebuliser solution (TNS) in adult and pediatric participants with cystic fibrosis (CF) and pulmonary 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	07 August 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	Netherlands: 3
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	United States: 95
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	274
EEA total number of subjects	174

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)	11
Adolescents (12-17 years)	49
Adults (18-64 years)	213
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Seventy-three sites in the United States (US) and European Union (EU) enrolled a total of 274 participants in the study.

Pre-assignment

Screening details:

274 participants enrolled in the study; 1 experienced a serious adverse event (SAE) and was not randomized; 273 were randomized; 268 were treated (136 AZLI; 132 TNS)

Period 1

Period 1 title	Randomized Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AZLI (75 mg TID)

Arm description:

Aztreonam 75 mg powder and diluent for nebuliser solution (AZLI) self-administered for 28 days for each treatment cycle

Arm type	Experimental
Investigational medicinal product name	Aztreonam 75 mg powder and diluent for nebuliser solution (AZLI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

AZLI (75 mg/1 mL aztreonam lysine when reconstituted in diluent [0.17% saline]; sterile, pH 4.2 to 7.0, and osmolality 300 to 550 mOsmol/kg) self-administered by inhalation three times a day (TID) using the PARI eFlow electronic investigational nebulizer

Arm title	TNS (300 mg BID)

Arm description:

Tobramycin nebulizer solution (TNS) self-administered for 28 days for each treatment cycle

Arm type	Active comparator
Investigational medicinal product name	Tobramycin nebulizer solution (TNS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

TNS (300 mg/5 mL) was self-administered by inhalation two times a day (BID) using the PARI LC PLUS(TM) Nebulizer with Compressor

Number of subjects in period 1[1]	AZLI (75 mg TID)	TNS (300 mg BID)
Started	136	132
Completed	124	111
Not completed	12	21
Physician decision	2	3
Unknown	-	1
Withdrawal by Subject	7	9
Safety or Tolerability	3	5
Lost to follow-up	-	1
Protocol deviation	-	2

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: Six participants who were enrolled but not treated are not included in the subject disposition table.

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label Extension

Arm description:

Eligible participants had the option to enter the Open-label Extension Phase to receive 3 additional courses of AZLI over a period of 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Aztreonam 75 mg powder and diluent for nebuliser solution (AZLI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

AZLI (75 mg/1 mL aztreonam lysine when reconstituted in diluent [0.17% saline]; sterile, pH 4.2 to 7.0, and osmolality 300 to 550 mOsmol/kg) self-administered by inhalation three times a day (TID) using the PARI eFlow electronic investigational nebulizer

Number of subjects in period 2[2]	Open-label Extension
Started	133
Completed	118
Not completed	15
Protocol violation	1

Safety or tolerability reasons	6
Subject relocated	1
Investigator's discretion	4
Withdrew consent	3

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: All eligible participants, including participants who discontinued early from the Randomized Phase, had the option to enter the Open-label Extension Phase (in the EU) to receive expanded access AZLI prior to its commercial availability.

Baseline characteristics

Reporting groups	
Reporting group title	AZLI (75 mg TID)
Reporting group description:	
Aztreonam 75 mg powder and diluent for nebuliser solution (AZLI) self-administered for 28 days for each treatment cycle	
Reporting group title	TNS (300 mg BID)
Reporting group description:	
Tobramycin nebulizer solution (TNS) self-administered for 28 days for each treatment cycle	

Reporting group values	AZLI (75 mg TID)	TNS (300 mg BID)	Total
Number of subjects	136	132	268
Age Categorical Units: participants			
≥ 6 years to ≤ 12 years	8	5	13
> 12 years to < 18 years	20	26	46
≥ 18 years	108	101	209
Age Continuous Units: years			
arithmetic mean	25.8	25.1	
standard deviation	± 9.1	± 9	-
Gender, Male/Female Units: participants			
Female	68	66	134
Male	68	66	134
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	130	131	261
More than one race	0	0	0
Unknown or Not Reported	5	0	5
Inhaled Tobramycin Use in the Previous 12 Months Units: Subjects			
< 84 days	21	19	40
≥ 84 days	115	113	228
Disease Severity			
Forced Expiratory Volume (FEV1) percent predicted is a normalized value of FEV1 calculated using the Knudson equation and based upon participant age, gender, and height. This baseline measure indicates the number of participants with FEV1 greater than 50% and less than or equal to 50% of the predicted value based on age, gender, and height at screening.			
Units: Subjects			
≤ 50% predicted	60	57	117
> 50% predicted	76	75	151

Body Mass Index (BMI) Units: kg/m^2 arithmetic mean standard deviation	 20.22 ± 2.95	 20.49 ± 2.82	 -
Cystic Fibrosis Questionnaire - Revised (CFQ-R) Respiratory Symptoms Scale (RSS) Score			
The CFQ-R is a validated, patient-reported outcome tool measuring health-related quality of life for children and adults with CF. The CFQ-R contains both general and CF-specific scales. Respiratory symptoms (e.g., coughing, congestion, wheezing) are 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 standard deviation	 62.87 ± 20.42	 58.02 ± 20.76	 -
Forced Expiratory Volume (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 standard deviation	 52.3 ± 15.56	 52.24 ± 14.57	 -

End points

End points reporting groups

Reporting group title	AZLI (75 mg TID)
Reporting group description:	
Aztreonam 75 mg powder and diluent for nebuliser solution (AZLI) self-administered for 28 days for each treatment cycle	
Reporting group title	TNS (300 mg BID)
Reporting group description:	
Tobramycin nebulizer solution (TNS) self-administered for 28 days for each treatment cycle	
Reporting group title	Open-label Extension
Reporting group description:	
Eligible participants had the option to enter the Open-label Extension Phase to receive 3 additional courses of AZLI over a period of 48 weeks.	

Primary: Relative Change from Baseline in Forced Expiratory Volume in 1 Second (FEV1) Percent Predicted at Day 28

End point title	Relative Change from Baseline in Forced Expiratory Volume in 1 Second (FEV1) Percent Predicted at Day 28
End point description:	
Spirometry was performed according to American Thoracic Society (ATS) guidelines at each visit. FEV1 percent predicted is a normalized value of FEV1 calculated using the Knudson equation and based upon participant age, gender, and height. Treatment effect on the relative change from baseline in FEV1 percent predicted at Day 28 (Visit 4) was tested using an analysis of covariance (ANCOVA) model-based method. Analysis was based on ITT population (all participants randomized to treatment who received at least part of one dose of study drug). The last observation carried forward (LOCF) method was used to impute missing data.	
End point type	Primary
End point timeframe:	
Baseline and end of treatment Course 1 (Day 28)	

End point values	AZLI (75 mg TID)	TNS (300 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	132		
Units: percent change in FEV1 percent predicted				
least squares mean (standard error)	8.35 (± 1.7)	0.55 (± 1.77)		

Statistical analyses

Statistical analysis title	AZLI vs TNS: Mean relative change of FEV1 percent
Statistical analysis description:	
Null hypothesis: AZLI was inferior to TNS by more than 4% in the mean relative change of FEV1 percent predicted at Day 28. With 120 subjects per treatment group there was at least 85% power to declare noninferiority based on relative change from baseline at Day 28 in FEV1 percent predicted using the	

upper bound of a 2-tailed 95% CI for the difference in means with a noninferiority margin of 4, assuming a common standard deviation of 18% and true difference in means [TNS-AZLI] of -3.2%.

Comparison groups	AZLI (75 mg TID) v TNS (300 mg BID)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.73
upper limit	-3.86

Notes:

[1] - The treatment difference (TNS-AZLI) and standard error from the ANCOVA model were used to compute the two-sided 95% confidence interval. If the 95% upper boundary was less than the pre-specified non-inferiority margin of 4%, then the null hypothesis was rejected. The non-inferiority statistical analysis type was requested by the EMA.

Primary: Mean Actual change from baseline in FEV1 percent predicted across 3 treatment courses

End point title	Mean Actual change from baseline in FEV1 percent predicted across 3 treatment courses

End point description:

Spirometry was performed according to ATS guidelines at each visit. FEV1 percent predicted is a normalized value of FEV1 calculated using the Knudson equation and based upon participant age, gender, and height.

Analysis was based on ITT population (all participants randomized to treatment who received at least part of one dose of study drug).

Treatment effect on the average adjusted means for the actual change in FEV1 percent predicted at Visits 4, 6, and 8 (Weeks 4, 12, and 20) was tested by mixed-effect model repeated measures (MMRM) analysis using the ITT population analysis set.

End point type	Primary

End point timeframe:

Baseline, and end of treatment Courses 1 (Week 4), 2 (Week 12), and 3 (Week 20)

End point values	AZLI (75 mg TID)	TNS (300 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	132		
Units: actual change in FEV1 percent predicted				
least squares mean (standard error)	2.05 (± 0.69)	-0.66 (± 0.72)		

Statistical analyses

Statistical analysis title	AZLI vs TNS: Mean actual change of FEV1 percent

Statistical analysis description:

Null hypothesis: there was no difference between AZLI and TNS treatment groups in the mean actual change of FEV1 percent predicted across 3 treatment courses among all participants.

With 120 subjects per treatment group, there was at least 90% power at a 5% significance level to detect differences based upon actual change from baseline in FEV1 percent predicted (3.61%, 2.98%, 2.32%) between AZLI and TNS at Weeks 4, 12, and 20 with a common standard deviation of 9%.

Comparison groups	AZLI (75 mg TID) v TNS (300 mg BID)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 [2]
Method	MMRM analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	-0.98

Notes:

[2] - Based on the Benjamini & Hochberg method, superiority at Weeks 4, 12, and 20 of actual change in FEV1 percent predicted was tested at the 0.05 level, given the significance of the coprimary endpoint ($p < 0.05$).

Secondary: Relative change from baseline in FEV1 percent predicted at Day 28 in subjects who received inhaled tobramycin for ≥ 84 days in the 12 months prior to randomization

End point title	Relative change from baseline in FEV1 percent predicted at Day 28 in subjects who received inhaled tobramycin for ≥ 84 days in the 12 months prior to randomization

End point description:

Spirometry was performed according to ATS guidelines. FEV1 percent predicted is a normalized value of FEV1 calculated using the Knudson equation and based upon participant age, gender, and height. Treatment effect on the relative change from baseline in FEV1 percent predicted at Day 28 (Visit 4) was tested using an ANCOVA model-based method, using the population of participants with prior inhaled tobramycin use of ≥ 84 days in the previous 12 months.

Analysis was based on participants with previous inhaled tobramycin use of ≥ 84 days within the previous 12 months using the ITT analysis set. The last observation carried forward (LOCF) method was used to impute missing data for statistical analyses.

End point type	Secondary

End point timeframe:

Baseline and end of treatment Course 1 (Day 28)

End point values	AZLI (75 mg TID)	TNS (300 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	113		
Units: percent change in FEV1 percent predicted				
least squares mean (standard error)	10.04 (± 1.56)	0.54 (± 1.57)		

Statistical analyses

Statistical analysis title	AZLI vs TNS: Mean relative change of FEV1 percent

Statistical analysis description:

Null hypothesis: AZLI was inferior to TNS by more than 4% in terms of the participant means in relative change of FEV1 percent predicted at Day 28 among all participants having ≥ 84 days of inhaled tobramycin use in the previous 12 months.

Comparison groups	AZLI (75 mg TID) v TNS (300 mg BID)
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.86
upper limit	-5.14

Notes:

[3] - The treatment difference (TNS-AZLI) and standard error from the ANCOVA model were used to compute the two-sided 95% confidence interval. If the 95% upper boundary was less than the pre-specified non-inferiority margin of 4%, then the null hypothesis was rejected.
[4] - Secondary endpoints were tested sequentially by the closed testing procedure initiated by the significance of the primary endpoints. Given the coprimary endpoints were met at the 0.05 level, this non-inferiority endpoint was tested at the 0.05 level.

Secondary: Mean Actual change from baseline in FEV1 percent predicted across 3 treatment courses in subjects who received inhaled tobramycin for ≥ 84 days in the 12 months prior to randomization

End point title	Mean Actual change from baseline in FEV1 percent predicted across 3 treatment courses in subjects who received inhaled tobramycin for ≥ 84 days in the 12 months prior to randomization

End point description:

Spirometry was performed according to ATS guidelines at each visit. FEV1 percent predicted is a normalized value of FEV1 calculated using the Knudson equation and based upon participant age, gender, and height.

Analysis was based on participants with prior inhaled tobramycin use ≥ 84 days in the previous 12 months using the ITT analysis set.

Treatment effect on the average adjusted means for the actual change in FEV1 percent predicted at Visits 4, 6, and 8 (Weeks 4, 12, and 20) was tested by MMRM analysis using the population of participants with prior inhaled tobramycin use of ≥ 84 days in the previous 12 months.

End point type	Secondary

End point timeframe:

Baseline and end of treatment Courses 1 (Week 4), 2 (Week 12), and 3 (Week 20)

End point values	AZLI (75 mg TID)	TNS (300 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	113		
Units: actual change in FEV1 percent predicted				
least squares mean (standard error)	3.26 (± 0.65)	-0.21 (± 0.66)		

Statistical analyses

Statistical analysis title	AZLI vs TNS: Mean actual change of FEV1 percent

Statistical analysis description:

Null hypothesis: there was no difference between AZLI and TNS treatment groups in the mean actual change of FEV1 percent predicted across 3 treatment courses in the stratum of subjects having ≥ 84 days of inhaled tobramycin use in the previous 12 months.

Comparison groups	AZLI (75 mg TID) v TNS (300 mg BID)
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0002 [6]
Method	MMRM analysis

Notes:

[5] - Comparative analysis

[6] - Secondary endpoints were tested sequentially to control the Type I error rate based on the closed testing procedure. Given the significance of the coprimary endpoints and previous secondary endpoint, this endpoint was also tested at the 0.05 level.

Secondary: Time to need for intravenous (IV) antipseudomonal antibiotics for respiratory events

End point title	Time to need for intravenous (IV) antipseudomonal antibiotics for respiratory events

End point description:

IV antipseudomonal antibiotic use for a respiratory event was determined through the adjudication of events by a sponsor-independent, blinded review committee.
Use was compiled from data recorded on the concomitant medications electronic case report form (eCRF) and compared to reported adverse events (AEs) to determine use for a respiratory event. The time to IV antipseudomonal antibiotic use was measured in days from baseline (Visit 2) to the date of first IV antipseudomonal antibiotic use or the date of study completion (last visit)/or early withdrawal if censored. Analysis was based on ITT population (all participants randomized to treatment who received at least part of one dose of study drug).

9999 = Median not reached due to insufficient number of events.
99999 = Upper limit of the 95% CI not reached due to insufficient number of events.

End point type	Secondary

End point timeframe:

Day 0 to Day 168 (end of study)

End point values	AZLI (75 mg TID)	TNS (300 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	132		
Units: days				
median (confidence interval 95%)	9999 (177 to 99999)	151 (113 to 99999)		

Statistical analyses

Statistical analysis title	AZLI vs TNS: Time needed for IV antibiotics

Statistical analysis description:

Null hypothesis: there was no difference between AZLI and TNS treatment groups with respect to time to need for IV antipseudomonal antibiotics for respiratory events.

Comparison groups	AZLI (75 mg TID) v TNS (300 mg BID)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0025 [8]
Method	Logrank

Notes:

[7] - Comparative analysis

[8] - Secondary endpoints were tested sequentially to control the Type I error rate based on the closed testing procedure. Given the significance of the coprimary endpoints and previous secondary endpoint, this endpoint was also tested at the 0.05 level.

Secondary: Time to first respiratory hospitalization

End point title	Time to first respiratory hospitalization

End point description:

This endpoint was determined through the adjudication of events by a sponsor-independent, blinded review committee. Committee members reviewed all hospitalizations and determined which were related to respiratory events. Analysis was based on ITT population (all participants randomized to treatment who received at least part of one dose of study drug).

Details of all hospitalizations, including the dates of admission and discharge, were recorded on the serious adverse event (SAE) eCRF.

Time to first respiratory hospitalization was the number of days from baseline (Visit 2) to the date of first respiratory hospitalization or the date of study completion (last visit) /or early withdrawal if censored.

999 = Lower limit of the 95% CI not reached due to insufficient number of events.
9999 = Median not reached due to insufficient number of events.
99999 = Upper limit of the 95% CI not reached due to insufficient number of events.

End point type	Secondary

End point timeframe:

Day 0 to Day 168 (end of study)

End point values	AZLI (75 mg TID)	TNS (300 mg BID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	132		
Units: days				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	AZLI vs TNS: Time to first resp hospitalization

Statistical analysis description:

Null hypothesis: there was no difference between AZLI and TNS treatment groups with respect to time to first respiratory hospitalization.

Comparison groups	AZLI (75 mg TID) v TNS (300 mg BID)
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1114 [9]
Method	Logrank

Notes:

[9] - Secondary endpoints were tested sequentially to control the Type I error rate based on the closed testing procedure. Given the significance of the coprimary endpoints and previous secondary endpoint, this endpoint was also tested at the 0.05 level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (AEs) were collected continuously from Day 0 (first dose) through Day 168 (Week 24), and for an additional 48 weeks during the optional extension phase (open-label AZLI).

Adverse event reporting additional description:

An AE was any physical/clinical worsening in symptoms/disease (including clinically significant change in lab values) experienced by a participant at any time during study, whether or not the AE was considered related to study participation or 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	AZLI (75 mg TID)

Reporting group description:

AZLI self-administered for 28 days for each treatment cycle

Reporting group title	TNS (300 mg BID)

Reporting group description:

TNS self-administered for 28 days for each treatment cycle

Reporting group title	Open-Label AZLI

Reporting group description: -

Serious adverse events	AZLI (75 mg TID)	TNS (300 mg BID)	Open-Label AZLI
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 136 (30.88%)	44 / 132 (33.33%)	35 / 133 (26.32%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hyperaemia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Vein Disorder			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
General disorders and administration site conditions			

Chest Discomfort			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Pain			
subjects affected / exposed	3 / 136 (2.21%)	2 / 132 (1.52%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exercise Tolerance Decreased			
subjects affected / exposed	6 / 136 (4.41%)	3 / 132 (2.27%)	9 / 133 (6.77%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 136 (0.74%)	3 / 132 (2.27%)	4 / 133 (3.01%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	0 / 136 (0.00%)	2 / 132 (1.52%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 136 (1.47%)	0 / 132 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	11 / 136 (8.09%)	8 / 132 (6.06%)	9 / 133 (6.77%)
occurrences causally related to treatment / all	0 / 13	0 / 10	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
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			
Cough			
subjects affected / exposed	27 / 136 (19.85%)	26 / 132 (19.70%)	22 / 133 (16.54%)
occurrences causally related to treatment / all	0 / 31	0 / 30	0 / 32
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	10 / 136 (7.35%)	15 / 132 (11.36%)	9 / 133 (6.77%)
occurrences causally related to treatment / all	1 / 13	0 / 17	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea Exertional			
subjects affected / exposed	1 / 136 (0.74%)	1 / 132 (0.76%)	0 / 133 (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
Haemoptysis			
subjects affected / exposed	5 / 136 (3.68%)	3 / 132 (2.27%)	6 / 133 (4.51%)
occurrences causally related to treatment / all	1 / 6	0 / 4	0 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Lung Infiltration			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal Congestion			

subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Nasal Mucosal Disorder			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Oropharyngeal Pain			
subjects affected / exposed	4 / 136 (2.94%)	0 / 132 (0.00%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic Pain			
subjects affected / exposed	0 / 136 (0.00%)	2 / 132 (1.52%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Productive Cough			
subjects affected / exposed	16 / 136 (11.76%)	23 / 132 (17.42%)	20 / 133 (15.04%)
occurrences causally related to treatment / all	1 / 20	0 / 29	0 / 28
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rales			
subjects affected / exposed	2 / 136 (1.47%)	3 / 132 (2.27%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Congestion			
subjects affected / exposed	1 / 136 (0.74%)	3 / 132 (2.27%)	4 / 133 (3.01%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinorrhoea			
subjects affected / exposed	3 / 136 (2.21%)	0 / 132 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhonchi			

subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Sinus Congestion			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Sputum Discoloured			
subjects affected / exposed	2 / 136 (1.47%)	1 / 132 (0.76%)	3 / 133 (2.26%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 136 (0.74%)	2 / 132 (1.52%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	3 / 136 (2.21%)	5 / 132 (3.79%)	4 / 133 (3.01%)
occurrences causally related to treatment / all	2 / 3	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial Secretion Retention			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Increased Bronchial Secretion			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
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			
Insomnia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Investigations			

Body Temperature Increased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breath Sounds Abnormal			
subjects affected / exposed	1 / 136 (0.74%)	1 / 132 (0.76%)	0 / 133 (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
C-Reactive Protein Increased			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Forced Expiratory Volume Decreased			
subjects affected / exposed	3 / 136 (2.21%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glycosylated Haemoglobin Increased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Oxygen Saturation Decreased			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	5 / 133 (3.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Function Test Decreased			
subjects affected / exposed	5 / 136 (3.68%)	4 / 132 (3.03%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	1 / 5	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	1 / 136 (0.74%)	2 / 132 (1.52%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Alcohol Poisoning			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Feeding Tube Complication			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Cyanosis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Tachycardia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Headache			
subjects affected / exposed	1 / 136 (0.74%)	1 / 132 (0.76%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	3 / 133 (2.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Poor Quality Sleep			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Sinus Headache			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	0 / 136 (0.00%)	2 / 132 (1.52%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Discomfort			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	5 / 136 (3.68%)	1 / 132 (0.76%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Nausea			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	4 / 136 (2.94%)	0 / 132 (0.00%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Diabetic Nephropathy			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Joint Swelling			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Muscle Spasms			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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

Pain in Extremity			
subjects affected / exposed	0 / 136 (0.00%)	1 / 132 (0.76%)	0 / 133 (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
Back Pain			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	2 / 133 (1.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Catheter Related Infection			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Systemic Candida			
subjects affected / exposed	1 / 136 (0.74%)	0 / 132 (0.00%)	0 / 133 (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
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	3 / 136 (2.21%)	2 / 132 (1.52%)	5 / 133 (3.76%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	2 / 136 (1.47%)	0 / 132 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorexia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 132 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
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 (75 mg TID)	TNS (300 mg BID)	Open-Label AZLI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 136 (90.44%)	125 / 132 (94.70%)	118 / 133 (88.72%)
Investigations			
Breath Sounds Abnormal			
subjects affected / exposed	7 / 136 (5.15%)	14 / 132 (10.61%)	5 / 133 (3.76%)
occurrences (all)	10	18	5
Forced Expiratory Volume Decreased			
subjects affected / exposed	7 / 136 (5.15%)	5 / 132 (3.79%)	4 / 133 (3.01%)
occurrences (all)	10	6	5
Pulmonary Function Test Decreased			
subjects affected / exposed	6 / 136 (4.41%)	15 / 132 (11.36%)	9 / 133 (6.77%)
occurrences (all)	8	18	10
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 136 (20.59%)	27 / 132 (20.45%)	21 / 133 (15.79%)
occurrences (all)	69	42	41
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	6 / 136 (4.41%)	8 / 132 (6.06%)	4 / 133 (3.01%)
occurrences (all)	6	11	5
Chest Discomfort			
subjects affected / exposed	13 / 136 (9.56%)	13 / 132 (9.85%)	4 / 133 (3.01%)
occurrences (all)	16	16	4
Exercise Tolerance Decreased			
subjects affected / exposed	20 / 136 (14.71%)	24 / 132 (18.18%)	8 / 133 (6.02%)
occurrences (all)	24	32	8
Fatigue			
subjects affected / exposed	23 / 136 (16.91%)	22 / 132 (16.67%)	8 / 133 (6.02%)
occurrences (all)	28	30	10
Pain			
subjects affected / exposed	9 / 136 (6.62%)	4 / 132 (3.03%)	1 / 133 (0.75%)
occurrences (all)	10	6	1
Pyrexia			
subjects affected / exposed	34 / 136 (25.00%)	36 / 132 (27.27%)	41 / 133 (30.83%)
occurrences (all)	55	52	62
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	15 / 136 (11.03%)	8 / 132 (6.06%)	9 / 133 (6.77%)
occurrences (all)	17	13	13
Diarrhoea			
subjects affected / exposed	4 / 136 (2.94%)	12 / 132 (9.09%)	13 / 133 (9.77%)
occurrences (all)	4	16	20
Nausea			
subjects affected / exposed	13 / 136 (9.56%)	10 / 132 (7.58%)	7 / 133 (5.26%)
occurrences (all)	15	14	7
Vomiting			
subjects affected / exposed	12 / 136 (8.82%)	14 / 132 (10.61%)	4 / 133 (3.01%)
occurrences (all)	15	15	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	92 / 136 (67.65%)	95 / 132 (71.97%)	81 / 133 (60.90%)
occurrences (all)	168	174	142
Dysphonia			
subjects affected / exposed	5 / 136 (3.68%)	8 / 132 (6.06%)	4 / 133 (3.01%)
occurrences (all)	5	10	4
Dyspnoea			
subjects affected / exposed	26 / 136 (19.12%)	28 / 132 (21.21%)	21 / 133 (15.79%)
occurrences (all)	32	45	25
Haemoptysis			
subjects affected / exposed	30 / 136 (22.06%)	20 / 132 (15.15%)	12 / 133 (9.02%)
occurrences (all)	45	32	20
Nasal Congestion			
subjects affected / exposed	29 / 136 (21.32%)	26 / 132 (19.70%)	10 / 133 (7.52%)
occurrences (all)	42	33	13
Oropharyngeal Pain			
subjects affected / exposed	34 / 136 (25.00%)	37 / 132 (28.03%)	20 / 133 (15.04%)
occurrences (all)	39	46	27
Productive Cough			
subjects affected / exposed	63 / 136 (46.32%)	67 / 132 (50.76%)	52 / 133 (39.10%)
occurrences (all)	94	108	71
Rales			

subjects affected / exposed	29 / 136 (21.32%)	32 / 132 (24.24%)	16 / 133 (12.03%)
occurrences (all)	32	43	23
Respiratory Tract Congestion			
subjects affected / exposed	15 / 136 (11.03%)	16 / 132 (12.12%)	7 / 133 (5.26%)
occurrences (all)	26	23	10
Rhinitis			
subjects affected / exposed	4 / 136 (2.94%)	7 / 132 (5.30%)	0 / 133 (0.00%)
occurrences (all)	5	7	0
Rhinorrhoea			
subjects affected / exposed	24 / 136 (17.65%)	33 / 132 (25.00%)	21 / 133 (15.79%)
occurrences (all)	31	37	27
Sinus Congestion			
subjects affected / exposed	3 / 136 (2.21%)	8 / 132 (6.06%)	1 / 133 (0.75%)
occurrences (all)	5	8	1
Wheezing			
subjects affected / exposed	13 / 136 (9.56%)	15 / 132 (11.36%)	8 / 133 (6.02%)
occurrences (all)	13	19	8
Musculoskeletal and connective tissue disorders			
Arthalgia			
subjects affected / exposed	10 / 136 (7.35%)	2 / 132 (1.52%)	9 / 133 (6.77%)
occurrences (all)	15	2	9
Back Pain			
subjects affected / exposed	7 / 136 (5.15%)	4 / 132 (3.03%)	4 / 133 (3.01%)
occurrences (all)	10	4	4
Myalgia			
subjects affected / exposed	9 / 136 (6.62%)	6 / 132 (4.55%)	2 / 133 (1.50%)
occurrences (all)	10	6	3
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	17 / 136 (12.50%)	17 / 132 (12.88%)	5 / 133 (3.76%)
occurrences (all)	21	20	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2007	Removed the requirement for previous inhaled tobramycin use in order to better reflect overall cystic fibrosis population and adjusted the sample size from 160 to 200 randomized to power the noninferiority analysis.
10 September 2008	Added an open label, single arm extension, to provide expanded access to AZLI prior to its commercial availability in the EU.
31 July 2009	Increased the study sample size from 200 subjects to 240 subjects to ensure adequate power for the primary superiority analysis and updated the statistical methods to reflect the change in primary analysis from noninferiority to superiority.
01 October 2009	To satisfy the requirements of the two health authorities, the analysis plan was revised to include coprimary endpoints: one for the EMA and one for the FDA. The noninferiority endpoint from the original protocol became a coprimary endpoint. Secondary endpoints were revised based on updated analysis plan. The sample size was increased to 240 subjects in order to adequately power these additional analyses.
12 February 2010	Revised one coprimary endpoint from relative change to actual change from baseline in FEV1 % predicted across 3 treatment courses among all subjects and added an over-enrollment threshold of 15% to the target enrollment of 240 subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported