Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Aztreonam for Inhalation Solution (AZLI) in a Continuous Alternating Therapy (CAT) Regimen of Inhaled Antibiotics for the Treatment of Chronic Pulmonary Pseudomonas aeruginosa Infection in Subjects with Cystic Fibrosis

Summary

EudraCT number	2015-000398-11
Trial protocol	Outside EU/EEA
Global end of trial date	15 January 2015

Results information

Result version number	v2 (current)
This version publication date	22 April 2016
First version publication date	31 July 2015
Version creation reason	• New data added to full data set • Correction of full data set Correction of data entry errors and descriptive text, and addition of "Age, categorical" to baseline characteristics.

Trial information

Trial identification

Sponsor protocol code	GS-US-205-0170

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01641822
WHO universal trial number (UTN)	-
Other trial identifiers	IND No: 064402, Clinical Trials.gov: NCT01641822

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	15 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and efficacy of a CAT regimen with aztreonam for inhalation solution (AZLI) and tobramycin inhalation solution (TIS) in adult and pediatric subjects with cystic fibrosis (CF) and pulmonary Pseudomonas aeruginosa (PA) infection. Participants were enrolled in a 28 day TIS run-in phase, and were eligible for randomization in the comparative phase if they had not received non-study oral antibiotics for a respiratory event or IV or inhaled antibiotics for any indication between Visits 2 and 3, had not developed a condition requiring hospitalization or other change in clinical status which, in the opinion of the investigator would preclude their ability to continue in the study, and had demonstrated at least 50% TIS compliance. Participants enrolled in the comparative phase were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: AZLI or placebo for 28 days followed by TIS for 28 days.

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	13 December 2012
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: 107
Worldwide total number of subjects	107
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)	6
Adolescents (12-17 years)	13
Adults (18-64 years)	87
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States. The first participant was screened on 13 December 2012. The last study visit occurred on 15 January 2015.

Pre-assignment

Screening details:

Following enrollment, participants received tobramycin inhalation solution (TIS) in the TIS Run-In Phase, and if still eligible were randomized 1 to 1 to receive aztreonam for inhalation solution (AZLI) or placebo to match AZLI alternating with TIS in the Comparative Phase.

Period 1

Period 1 title	TIS Run-In Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	TIS Run-In Treatment Group

Arm description:

Enrolled participants received 28 days of TIS during the run-in phase.

Arm type	Standard of care
Investigational medicinal product name	Tobramycin inhalation solution
Investigational medicinal product code	
Other name	TIS, TOBI®
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

TIS 300 mg 2 times daily using a PARI® LC Plus nebulizer and DeVilbiss Pulmo-Aide® air compressor

Number of subjects in period 1	TIS Run-In Treatment Group
Started	107
Completed	93
Not completed	14
Adverse event, non-fatal	3
Protocol-specified criteria for withdrawal	9
Noncompliance with study drug	1
Withdrew consent	1

Period 2

Period 2 title	Comparative Phase
Is this the baseline period?	Yes[1]
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 were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: AZLI for 28 days followed by TIS for 28 days.

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 3 times daily combined with diluent administered using an eFlow nebulizer

Investigational medicinal product name	Tobramycin inhalation solution
Investigational medicinal product code	
Other name	TIS, TOBI®
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

TIS 300 mg 2 times daily using a PARI® LC Plus nebulizer and DeVilbiss Pulmo-Aide® air compressor

Arm title	Placebo

Arm description:

Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: placebo to match AZLI for 28 days followed by TIS for 28 days.

Arm type	Active comparator
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 3 times daily combined with diluent administered using an eFlow nebulizer

Investigational medicinal product name	Tobramycin inhalation solution
Investigational medicinal product code	
Other name	TIS, TOBI®
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

TIS 300 mg 2 times daily using a PARI® LC Plus nebulizer and DeVilbiss Pulmo-Aide® air compressor

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The TIS Run-In Phase (Period 1) was a period to determine eligibility in the randomized comparative phase (Period 2). The comparative phase was
the primary phase of the study and the baseline period.

Number of subjects in period 2[2][3]	AZLI	Placebo
Started	43	47
Completed	37	37
Not completed	6	10
Adverse event, serious fatal	1	-
Protocol-specified criteria for withdrawal	1	1
Pregnancy	-	1
Noncompliance with study drug	1	-
Withdrew consent	3	7
Investigator's discretion	-	1

Notes:

[2] - 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: 107 participants were enrolled (worldwide) and entered the TIS Run-In Phase. 17 participants were not eligible to enter the comparative phase
(baseline period).
[3] - 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: 17 participants enrolled in the TIS Run-In Phase were not eligible to enter the comparative phase.

Baseline characteristics

Reporting groups	
Reporting group title	AZLI
Reporting group description:	
Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: AZLI for 28 days followed by TIS for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: placebo to match AZLI for 28 days followed by TIS for 28 days.	

Reporting group values	AZLI	Placebo	Total
Number of subjects	43	47	90
Age categorical Units: Subjects			
6 - 12 years	3	1	4
13 - 17 years	5	6	11
≥ 18 years	35	40	75
Age continuous Units: years			
arithmetic mean	28.8	28	
standard deviation	± 12.1	± 10.88	-
Gender categorical Units: Subjects			
Female	24	28	52
Male	19	19	38
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
White	41	45	86
Other	2	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	5	4	9
Not Hispanic or Latino	38	43	81
FEV1 % predicted at Day 1			
FEV1 is defined as the maximal volume of air that can be exhaled in 1 second. FEV1 % predicted is defined as FEV1 of the participant divided by the average FEV1 in the population for any person of similar age, sex, race, and body composition.			
Units: percentage of FEV1 % predicted			
arithmetic mean	49.95	50.25	
standard deviation	± 17.5	± 15.131	-
CFQ-R Respiratory Score at Day 1			
Respiratory symptoms (eg, coughing, congestion, wheezing) were assessed with the Cystic Fibrosis Questionnaire - Revised (CFQ-R) Respiratory Symptoms Scale (RSS). The range of scores (units) was 0 to 100 with higher scores indicating fewer symptoms.			
Units: units on a scale			
arithmetic mean	59.72	64.24	
standard deviation	± 18.408	± 15.044	-

End points

End points reporting groups

Reporting group title	TIS Run-In Treatment Group
Reporting group description:	
Enrolled participants received 28 days of TIS during the run-in phase.	
Reporting group title	AZLI
Reporting group description:	
Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: AZLI for 28 days followed by TIS for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: placebo to match AZLI for 28 days followed by TIS for 28 days.	

Primary: Rate of protocol-defined exacerbations (PDE) from baseline through Week 24

End point title	Rate of protocol-defined exacerbations (PDE) from baseline through Week 24
End point description:	
PDEs were characterized by a change or worsening from baseline of 1 or more documented signs or symptoms (decreased exercise tolerance, increased cough, increased sputum or chest congestion, decreased appetite, or other signs or symptoms) associated with the use of non-study IV or inhaled antibiotics and be verified by a blinded independent adjudication committee.	
End point type	Primary
End point timeframe:	
Baseline in the comparative phase to the end of study (average time on study during the Comparative Phase: 155.4 days)	

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	47		
Units: PDEs per participant year				
number (not applicable)	1.309	1.762		

Statistical analyses

Statistical analysis title	Ratio between rates
Comparison groups	Placebo v AZLI

Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Negative binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.743
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.446
upper limit	1.238

Secondary: Average actual change from baseline in FEV1 % predicted across all courses of AZLI/placebo treatment (Weeks 4, 12 and 20)

End point title	Average actual change from baseline in FEV1 % predicted across all courses of AZLI/placebo treatment (Weeks 4, 12 and 20)

End point description:

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.

The adjusted mean is from a mixed-effect model repeated measures (MMRM) analysis. The model includes terms for baseline value, previous exacerbations (1, 2, ≥ 3), treatment, visit (categorical), and treatment by visit interaction.

End point type	Secondary

End point timeframe:

Comparative Phase: Baseline and Weeks 4, 12, and 20

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	45		
Units: percentage of FEV1 % predicted				
least squares mean (standard error)	1.37 (± 0.674)	0.04 (± 0.658)		

Statistical analyses

Statistical analysis title	Difference in change in FEV1 % predicted
Comparison groups	AZLI v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.16 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	3.2

Notes:

[1] - Intergroup analysis

[2] - The p-value is from an MMRM analysis. The model includes terms for baseline value, previous exacerbations (1, 2, ≥ 3), treatment, visit (categorical), and treatment by visit interaction.

Secondary: Percentage of participants who used non-study IV or inhaled antibiotics for protocol-defined pulmonary exacerbations

End point title	Percentage of participants who used non-study IV or inhaled antibiotics for protocol-defined pulmonary exacerbations

End point description:

End point type	Secondary

End point timeframe:

Baseline in the comparative phase to the end of study (average time on study during the Comparative Phase: 155.4 days)

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	47		
Units: percentage of participants				
number (not applicable)	48.8	55.3		

Statistical analyses

Statistical analysis title	Comparison of percentages
Comparison groups	AZLI v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.67
Method	Fisher exact

Notes:

[3] - Intergroup analysis

Secondary: Time to first protocol-defined pulmonary exacerbation

End point title	Time to first protocol-defined pulmonary exacerbation

End point description:

The time to first protocol-defined pulmonary exacerbation was calculated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Baseline in the comparative phase to the end of study (average time on study during the Comparative

Phase: 155.4 days)

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	47		
Units: median days	175	140		

Statistical analyses

Statistical analysis title	Comparison of time to exacerbation
Comparison groups	AZLI v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.71
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.59

Secondary: Rate of Hospitalization for a Respiratory Event

End point title	Rate of Hospitalization for a Respiratory Event

End point description:

The rate of hospitalizations for a respiratory event per participant year was calculated using negative binomial regression analysis.

End point type	Secondary

End point timeframe:

Baseline in the comparative phase to the end of study (average time on study during the Comparative Phase: 155.4 days)

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	47		
Units: hospitalizations per participant year				
number (not applicable)	1.043	1.624		

Statistical analyses

Statistical analysis title	Comparison of hospitalization rate
Comparison groups	AZLI v Placebo
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.14
Method	Negative binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.642
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.355
upper limit	1.164

Notes:

[4] - Intergroup analysis

Secondary: Average change from baseline in the CFQ-R Respiratory Symptom Scale (RSS) score across all courses of AZLI/placebo treatment (Weeks 4, 12 and 20)

End point title	Average change from baseline in the CFQ-R Respiratory Symptom Scale (RSS) score across all courses of AZLI/placebo treatment (Weeks 4, 12 and 20)

End point description:

Respiratory symptoms (eg, coughing, congestion, wheezing) were assessed with the Cystic Fibrosis Questionnaire - Revised (CFQ-R) Respiratory Symptoms Scale (RSS). The range of scores (units) was 0 to 100 with higher scores indicating fewer symptoms.

The adjusted mean is from a mixed-effect model repeated measures (MMRM) analysis. The model includes terms for baseline value, previous exacerbations (1, 2, ≥ 3), treatment, visit (categorical), and treatment by visit interaction.

End point type	Secondary

End point timeframe:

Comparative Phase: Baseline and Weeks 4, 12, and 20

End point values	AZLI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	45		
Units: units on a scale				
least squares mean (standard deviation)	1 (± 1.736)	-2.06 (± 1.629)		

Statistical analyses

Statistical analysis title	Difference in change in CFQ-R RSS
Comparison groups	AZLI v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.21 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	7.82

Notes:

[5] - Intergroup analysis

[6] - The p-value is from an MMRM analysis. The model includes terms for baseline value, previous exacerbations (1, 2, ≥ 3), treatment, visit (categorical), and treatment by visit interaction.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TIS Run-In Treatment Group: up to 28 days (plus 30 days if not continuing to the comparative phase). Comparative phase: from first dose of AZLI or Placebo through 30 days after last dose (average 155.4 days).

Adverse event reporting additional description:

Safety analysis set: participants who were enrolled and received at least 1 dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	TIS Run-In Treatment Group (in Run-In Phase)

Reporting group description:

Adverse events reported in this group are those experienced by participants during in the 28-day run-in TIS treatment phase.

Reporting group title	Placebo (in Comparative Phase)

Reporting group description:

Adverse events reported in this group are those experienced by participants who were randomized to placebo in the comparative phase (after having completed the 28-day run-in TIS treatment phase) and received at least 1 dose of study drug.

Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: placebo to match AZLI for 28 days followed by TIS for 28 days.

Reporting group title	AZLI (in Comparative Phase)

Reporting group description:

Adverse events reported in this group are those experienced by participants who were randomized to AZLI in the comparative phase (after having completed the 28-day run-in TIS treatment phase) and received at least 1 dose of study drug.

Participants were randomized to receive 3 cycles of treatment, each cycle consisting alternating regimens: AZLI for 28 days followed by TIS for 28 days.

Serious adverse events	TIS Run-In Treatment Group (in Run-In Phase)	Placebo (in Comparative Phase)	AZLI (in Comparative Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 107 (3.74%)	24 / 46 (52.17%)	21 / 42 (50.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Joint dislocation			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Postoperative respiratory failure			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Upper limb fracture			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
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 upper			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
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			
Cholelithiasis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
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			
Lung disorder			
subjects affected / exposed	1 / 107 (0.93%)	13 / 46 (28.26%)	9 / 42 (21.43%)
occurrences causally related to treatment / all	0 / 1	0 / 18	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Respiratory disorder			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Respiratory failure			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
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			
Nephrolithiasis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 107 (1.87%)	5 / 46 (10.87%)	9 / 42 (21.43%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 107 (0.00%)	3 / 46 (6.52%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 107 (0.93%)	1 / 46 (2.17%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Gastroenteritis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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 exacerbation of bronchiectasis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	0 / 42 (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
Pseudomonal bacteraemia			

subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	1 / 42 (2.38%)
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	TIS Run-In Treatment Group (in Run-In Phase)	Placebo (in Comparative Phase)	AZLI (in Comparative Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 107 (25.23%)	44 / 46 (95.65%)	38 / 42 (90.48%)
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 107 (0.00%)	10 / 46 (21.74%)	11 / 42 (26.19%)
occurrences (all)	0	12	13
Weight decreased			
subjects affected / exposed	0 / 107 (0.00%)	5 / 46 (10.87%)	4 / 42 (9.52%)
occurrences (all)	0	5	7
Forced expiratory volume decreased			
subjects affected / exposed	0 / 107 (0.00%)	2 / 46 (4.35%)	4 / 42 (9.52%)
occurrences (all)	0	2	5
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 107 (0.00%)	8 / 46 (17.39%)	7 / 42 (16.67%)
occurrences (all)	0	10	8
Sinus headache			
subjects affected / exposed	0 / 107 (0.00%)	2 / 46 (4.35%)	3 / 42 (7.14%)
occurrences (all)	0	2	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 107 (5.61%)	17 / 46 (36.96%)	11 / 42 (26.19%)
occurrences (all)	6	20	17
Chest discomfort			
subjects affected / exposed	7 / 107 (6.54%)	13 / 46 (28.26%)	8 / 42 (19.05%)
occurrences (all)	7	15	8
Exercise tolerance decreased			
subjects affected / exposed	0 / 107 (0.00%)	12 / 46 (26.09%)	3 / 42 (7.14%)
occurrences (all)	0	14	3
Chest pain			
subjects affected / exposed	0 / 107 (0.00%)	7 / 46 (15.22%)	4 / 42 (9.52%)
occurrences (all)	0	9	5
Chills			
subjects affected / exposed	0 / 107 (0.00%)	5 / 46 (10.87%)	3 / 42 (7.14%)
occurrences (all)	0	5	5
Pyrexia			
subjects affected / exposed	0 / 107 (0.00%)	13 / 46 (28.26%)	8 / 42 (19.05%)
occurrences (all)	0	17	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 107 (0.00%)	10 / 46 (21.74%)	6 / 42 (14.29%)
occurrences (all)	0	14	9
Vomiting			
subjects affected / exposed	0 / 107 (0.00%)	9 / 46 (19.57%)	5 / 42 (11.90%)
occurrences (all)	0	11	7
Diarrhoea			
subjects affected / exposed	0 / 107 (0.00%)	5 / 46 (10.87%)	6 / 42 (14.29%)
occurrences (all)	0	5	7
Abdominal pain			

subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	4 / 42 (9.52%)
occurrences (all)	0	1	5
Constipation			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 107 (19.63%)	33 / 46 (71.74%)	32 / 42 (76.19%)
occurrences (all)	21	67	52
Sputum increased			
subjects affected / exposed	12 / 107 (11.21%)	31 / 46 (67.39%)	20 / 42 (47.62%)
occurrences (all)	12	51	32
Dyspnoea			
subjects affected / exposed	9 / 107 (8.41%)	24 / 46 (52.17%)	13 / 42 (30.95%)
occurrences (all)	9	38	25
Haemoptysis			
subjects affected / exposed	0 / 107 (0.00%)	11 / 46 (23.91%)	11 / 42 (26.19%)
occurrences (all)	0	12	15
Respiratory tract congestion			
subjects affected / exposed	0 / 107 (0.00%)	11 / 46 (23.91%)	11 / 42 (26.19%)
occurrences (all)	0	12	14
Wheezing			
subjects affected / exposed	6 / 107 (5.61%)	9 / 46 (19.57%)	9 / 42 (21.43%)
occurrences (all)	6	10	9
Nasal congestion			
subjects affected / exposed	0 / 107 (0.00%)	4 / 46 (8.70%)	11 / 42 (26.19%)
occurrences (all)	0	4	12
Rhinorrhoea			
subjects affected / exposed	0 / 107 (0.00%)	8 / 46 (17.39%)	5 / 42 (11.90%)
occurrences (all)	0	8	6
Oropharyngeal pain			
subjects affected / exposed	0 / 107 (0.00%)	5 / 46 (10.87%)	6 / 42 (14.29%)
occurrences (all)	0	5	8
Sinus congestion			

subjects affected / exposed	0 / 107 (0.00%)	7 / 46 (15.22%)	3 / 42 (7.14%)
occurrences (all)	0	10	4
Sputum discoloured			
subjects affected / exposed	0 / 107 (0.00%)	3 / 46 (6.52%)	5 / 42 (11.90%)
occurrences (all)	0	3	7
Dyspnoea exertional			
subjects affected / exposed	0 / 107 (0.00%)	2 / 46 (4.35%)	5 / 42 (11.90%)
occurrences (all)	0	3	8
Dysphonia			
subjects affected / exposed	0 / 107 (0.00%)	2 / 46 (4.35%)	4 / 42 (9.52%)
occurrences (all)	0	2	4
Upper-airway cough syndrome			
subjects affected / exposed	0 / 107 (0.00%)	4 / 46 (8.70%)	2 / 42 (4.76%)
occurrences (all)	0	5	3
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 107 (0.00%)	4 / 46 (8.70%)	1 / 42 (2.38%)
occurrences (all)	0	5	2
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 107 (0.00%)	3 / 46 (6.52%)	1 / 42 (2.38%)
occurrences (all)	0	3	1
Rales			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	3 / 42 (7.14%)
occurrences (all)	0	1	4
Pleuritic pain			
subjects affected / exposed	0 / 107 (0.00%)	3 / 46 (6.52%)	0 / 42 (0.00%)
occurrences (all)	0	3	0
Productive cough			
subjects affected / exposed	0 / 107 (0.00%)	3 / 46 (6.52%)	0 / 42 (0.00%)
occurrences (all)	0	6	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	4 / 42 (9.52%)
occurrences (all)	0	1	4
Pruritus			

subjects affected / exposed	0 / 107 (0.00%)	1 / 46 (2.17%)	3 / 42 (7.14%)
occurrences (all)	0	1	3
Night sweats			
subjects affected / exposed	0 / 107 (0.00%)	0 / 46 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 107 (0.00%)	3 / 46 (6.52%)	3 / 42 (7.14%)
occurrences (all)	0	3	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 107 (0.00%)	4 / 46 (8.70%)	3 / 42 (7.14%)
occurrences (all)	0	5	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 107 (0.00%)	16 / 46 (34.78%)	5 / 42 (11.90%)
occurrences (all)	0	21	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2012	Use of the Cystic Fibrosis Respiratory Symptom Diary (CFRSD) was added; clarification that participants who experienced a protocol-defined exacerbation (PDE) after Visit 3 and took antibiotics were expected to remain on study; the definition of PDE was clarified as a change or worsening from baseline of 1 or more documented signs or symptoms (decreased exercise tolerance, increased cough, increased sputum or chest congestion, decreased appetite, or other signs or symptoms) associated with the use of nonstudy antibiotics, and had to be verified by a blinded independent adjudication committee; the study duration was increased from 24 weeks to 28 weeks to include the 4-week TIS run-in phase.
08 August 2012	The primary endpoint definition was clarified by adding 'IV or inhaled' to nonstudy antibiotic use throughout protocol document; Sample Cystic Fibrosis Questionnaire–Revised (CFQ-R) and European Questionnaire-5 Dimensions (EQ-5D) were added.
21 March 2013	Throat swab cultures were allowed to document history of PA infection.

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: