Clinical trial results:
Open-Label Phase 3 Trial to Evaluate the Safety of Aztreonam 75 mg Powder and Solvent for Nebuliser Solution/Aztreonam for Inhalation Solution (AZLI) in Children With Cystic Fibrosis (CF) and Chronic Pseudomonas Aeruginosa (PA) in the Lower Airways

Summary

EudraCT number	2011-001362-18
Trial protocol	DE ES FR IT Outside EU/EEA
Global end of trial date	03 April 2013

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-205-0160

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01404234
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	03 April 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was an open-label, multicenter study in children ≤ 12 years of age with cystic fibrosis (CF) and chronic Pseudomonas aeruginosa (PA) infection in the lower airways using three 28-day courses of Aztreonam for Inhalation Solution (AZLI) 75 mg three times daily, each followed by 28 days off AZLI. The total treatment duration was to be 6 months.

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	29 December 2011
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	Poland: 11
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	61
EEA total number of subjects	32

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)	2
Children (2-11 years)	45
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at a total of 25 study sites in the United States and Europe. The first participant was screened on 29 December 2011. The last participant observation was on 03 April 2013.

Pre-assignment

Screening details:

74 participants were screened; 61 participants were enrolled and treated, and comprise the Safety Analysis Set and the Full Analysis Set.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AZLI

Arm description:

Participants received three 28-day courses of AZLI, each followed by 28 days off-treatment. AZLI 75 mg was administered 3 times daily via the investigational nebulizer.

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

Dosage and administration details:

Aztreonam for Inhalation solution (AZLI) 75 mg powder and solvent for nebuliser solution administered via the investigational nebulizer at a minimum of 4 hours between doses.

Number of subjects in period 1	AZLI
Started	61
Completed	59
Not completed	2
Withdrawal by Subject	2

Baseline characteristics

Reporting groups	
Reporting group title	AZLI
Reporting group description:	
Participants received three 28-day courses of AZLI, each followed by 28 days off-treatment. AZLI 75 mg was administered 3 times daily via the investigational nebulizer.	

Reporting group values	AZLI	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
< 2 years	2	2	
≥ 2 years to < 6 years	7	7	
≥ 6 years to ≤ 12 years	52	52	
Age continuous Units: years			
arithmetic mean	9		
standard deviation	± 2.94	-	
Gender categorical Units: Subjects			
Female	31	31	
Male	30	30	
Ethnicity Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	55	55	
Unknown or not reported	1	1	
Race Units: Subjects			
Black or African heritage	2	2	
White	55	55	
Other	3	3	
Not permitted	1	1	
Presence of Pseudomonas aeruginosa (PA) Units: Subjects			
Present	58	58	
Absent	3	3	
Body mass index Units: kg/m^2			
arithmetic mean	16.3		
standard deviation	± 1.66	-	
Forced expiratory volume in 1 second (FEV1) % 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, race, and body composition. Participants ≥ 6 years of age were analyzed at baseline for FEV1 % predicted (n = 52).			
Units: percentage of FEV1 % predicted			
arithmetic mean	80.31		

standard deviation	± 19.494	-	
FEV1			
FEV1 is defined as the maximal volume of air that can be exhaled in 1 second. Participants ≥ 6 years of age were analyzed at baseline for FEV1 (n = 52).			
Units: litre(s)			
arithmetic mean	1.67		
standard deviation	± 0.627	-	
Forced vital capacity (FVC)			
FVC is defined as the volume of air that can forcibly be blown out after taking a full breath. Participants ≥ 6 years of age were analyzed at baseline for FVC (n = 52).			
Units: litre(s)			
arithmetic mean	2.11		
standard deviation	± 0.687	-	
FEV25-75			
FEV25-75 is defined as the forced expiratory flow from 25% to 75% of the FVC. Participants ≥ 6 years of age were analyzed at baseline for FEV25-75 (n = 52).			
Units: litres per second			
arithmetic mean	1.82		
standard deviation	± 1.169	-	
CFQ-R RSS Score			
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. Participants ≥ 6 years of age were analyzed at baseline for CFQ-R RSS (n = 51; data was missing for one participant).			
Units: units on a scale			
arithmetic mean	71.73		
standard deviation	± 17.327	-	

End points

End points reporting groups

Reporting group title	AZLI

Reporting group description:

Participants received three 28-day courses of AZLI, each followed by 28 days off-treatment. AZLI 75 mg was administered 3 times daily via the investigational nebulizer.

Primary: Percentage of Participants Who Discontinued Study Drug Due to Safety or Tolerability Reasons

End point title	Percentage of Participants Who Discontinued Study Drug Due to Safety or Tolerability Reasons[1]

End point description:

Participants who discontinued study drug due to safety or tolerability reasons were defined as those with "Adverse Event (AE)/Safety or Tolerability" on the Study Drug Completion electronic case report form as the reason for early discontinuation. The 95% confidence interval (CI) was calculated using the exact binomial method.
Two participants voluntarily withdrew from the study prior to completion (not due to AEs/safety or tolerability reasons) and were not included in the analysis.

End point type	Primary

End point timeframe:

Baseline to Day 168

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No intergroup analysis was performed because the study was single-arm, and no analysis against a historic rate was performed because the study was not designed to demonstrate superiority or noninferiority.

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FEV1 % Predicted in Subjects Aged ≥ 6 Years

End point title	Change From Baseline in FEV1 % Predicted in Subjects Aged ≥ 6 Years

End point description:

The change in FEV1 % predicted was assessed at the end of each 28-day AZLI treatment course.
FEV1 % predicted is defined as FEV1 of the patient divided by the average FEV1 in the population for any person of similar age, sex, race, and body composition.
Participants ≥ 6 years of age were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Day 28, 84, and 140

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: percentage of FEV1 % predicted				
arithmetic mean (standard deviation)				
Change at Day 28 (on-treatment, n = 52)	4.73 (± 11.703)			
Change at Day 84 (on-treatment, n = 51)	1.72 (± 12.516)			
Change at Day 140 (on-treatment, n = 50)	1.65 (± 10.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CFQ-R Respiratory Symptoms Scale (RSS) Score in Subjects Aged ≥ 6 Years

End point title	Change From Baseline in CFQ-R Respiratory Symptoms Scale (RSS) Score in Subjects Aged ≥ 6 Years

End point description:

The change in CFQ-R RSS score was assessed at the end of each 28-day AZLI treatment course. The range of scores (units) was 0 to 100 with higher scores indicating fewer symptoms. Participants ≥ 6 years of age were analyzed.

End point type	Secondary

End point timeframe:

Baseline to Day 28, 84, and 140

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Day 28 (on-treatment, n = 51)	8.66 (± 14.903)			
Change at Day 84 (on-treatment, n = 48)	9.38 (± 18.243)			
Change at Day 140 (on-treatment, n = 48)	5.9 (± 15.372)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pseudomonas Aeruginosa (PA) Sputum Density

End point title	Change in Pseudomonas Aeruginosa (PA) Sputum Density

End point description:

The change in PA sputum density (log10 colony-forming units per gram [cfu/g]) was assessed at the end of each 28-day AZLI treatment course.

End point type	Secondary

End point timeframe:

Baseline to Day 28, 84, and 140

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: log10 CFU/g				
arithmetic mean (standard deviation)				
Change at Day 28 (on-treatment, n = 24)	-2.6 (± 2.5)			
Change at Day 84 (on-treatment, n = 25)	-2 (± 2.14)			
Change at Day 140 (on-treatment, n = 23)	-1.2 (± 2.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Used Additional (Non-study) Antipseudomonal Antibiotics

End point title	Percentage of Participants Who Used Additional (Non-study) Antipseudomonal Antibiotics

End point description:

The percentage of participants who used additional (non-study) antipseudomonal antibiotics (IV, inhaled, oral, IV/inhaled, IV/inhaled/oral) was summarized (number and percent) for all subjects.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: percentage of participants				
number (not applicable)				
Never used non-study antipseudomonal antibiotics	42.6			

Used non-study antipseudomonal antibiotics	57.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Hospitalized at Least Once Due to a Respiratory Event

End point title	Percentage of Participants Hospitalized at Least Once Due to a Respiratory Event

End point description:

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: percentage of participants				
number (not applicable)				
Never hospitalized	82			
Hospitalized at least once	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Participants Were Hospitalized Due to a Respiratory Event

End point title	Number of Days Participants Were Hospitalized Due to a Respiratory Event

End point description:

The average number of days hospitalized due to a respiratory event, among the 11 participants who were hospitalized for respiratory event, was reported.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: days				
arithmetic mean (standard deviation)	12.6 (± 8.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pulmonary Exacerbations

End point title	Percentage of Participants With Pulmonary Exacerbations

End point description:

Pulmonary exacerbations were defined as respiratory hospitalizations or discrete courses of non-study IV/inhaled antipseudomonal antibiotics. Use of oral antibiotics alone for respiratory signs or symptoms was considered to be representative of milder clinical events and, therefore, was not included in the definition of pulmonary exacerbations.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: percentage of participants				
number (not applicable)				
No pulmonary exacerbation	62.3			
At least one pulmonary exacerbation	37.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pulmonary Exacerbation

End point title	Time to Pulmonary Exacerbation

End point description:

The median days to first pulmonary exacerbation was summarized using Kaplan-Meier (KM) summary statistics.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: median days	176			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Study-drug Induced Bronchospasm

End point title	Percentage of Participants With Study-drug Induced Bronchospasm

End point description:

Study-drug induced bronchospasm (airway reactivity) was assessed at the baseline visit as the percent change in FEV1 from the pretreatment measurement to 30 minutes following treatment for subjects ≥ 6 years or as from the Investigator's assessment for subjects < 6 years.

End point type	Secondary

End point timeframe:

Pretreatment at Baseline to 30 minutes following treatment

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: percentage of participants				
number (not applicable)	3.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Event Rates Adjusted for Study Duration

End point title	Adverse Event Rates Adjusted for Study Duration

End point description:

Adverse events occurring in ≥ 5% of participants adjusted for study duration were summarized. The adjustment was made by using a standardized rate calculated as the sum of study duration across patients divided by 28 for the total number of patient months. Rate calculations presented are the number of adverse events (AEs) per patient month.

End point type	Secondary

End point timeframe:

Baseline to Day 168

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	61			
Units: AEs (per patient month)				
number (not applicable)				
Cough	0.163			
Nasal congestion	0.05			
Rhinnorrhoea	0.041			
Wheezing	0.033			
Sputum increased	0.033			
Productive cough	0.03			
Lung disorder	0.025			
Haemoptysis	0.019			
Rhonchi	0.019			
Oropharyngeal pain	0.017			
Rales	0.017			
Respiratory tract congestion	0.014			
Abdominal pain	0.03			
Diarrhoea	0.019			
Vomiting	0.019			
Abdominal pain upper	0.017			
Pyrexia	0.061			
Fatigue	0.025			
Rhinitis	0.03			
Pulmonary function test decreased	0.014			
Forced expiratory volume decreased	0.011			
Decreased appetite	0.017			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Day 168

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	AZLI

Reporting group description:

Participants received three 28-day courses of AZLI, each followed by 28 days off-treatment. AZLI 75 mg was administered 3 times daily via the investigational nebulizer.

Serious adverse events	AZLI		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 61 (21.31%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Appendiceal mucocoele			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			

subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 61 (3.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	AZLI		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 61 (81.97%)		
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Pulmonary function test decreased			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 61 (13.11%)		
occurrences (all)	9		
Pyrexia			

subjects affected / exposed	16 / 61 (26.23%)		
occurrences (all)	22		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	9		
Abdominal pain upper			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 61 (59.02%)		
occurrences (all)	58		
Haemoptysis			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	7		
Nasal congestion			
subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	16		
Oropharyngeal pain			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
Productive cough			
subjects affected / exposed	8 / 61 (13.11%)		
occurrences (all)	11		
Rales			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences (all)	6		
Respiratory tract congestion			

subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Rhonchi subjects affected / exposed occurrences (all) Sputum increased subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5 10 / 61 (16.39%) 15 6 / 61 (9.84%) 7 9 / 61 (14.75%) 12 9 / 61 (14.75%) 12		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	10 / 61 (16.39%) 11		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 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

None reported