Clinical trial results:
Open-Label Phase 2 Trial to Evaluate the Safety and Efficacy of Aztreonam 75 mg Powder and Solvent for Nebuliser Solution/Aztreonam for Inhalation Solution (AZLI) in Pediatric Patients with Cystic Fibrosis (CF) and New Onset Lower Respiratory Tract Culture Positive for Pseudomonas aeruginosa (PA)

Summary

EudraCT number	2011-001255-36
Trial protocol	DE BE FR AT ES NL IE IT Outside EU/EEA
Global end of trial date	29 May 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-205-0162

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01375049
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	29 May 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an open-label, multi-center study in pediatric patients age 3 months to less than 18 years with cystic fibrosis (CF) and newly detected Pseudomonas
aeruginosa (PA) pulmonary colonization/infection. All eligible participants will be treated with a 28-day course of Aztreonam for Inhalation Solution (AZLI) 75 mg 3
times daily. After completion of study drug, subjects will be followed up through Day 196 for safety and recurrence of PA.

The primary objective is to evaluate the proportion of participants with PA-negative cultures at all time points during a 6-month monitoring period (through Day
196) after cessation of AZLI treatment. Microbiological cultures will be obtained at Baseline, Day 28 (end of AZLI treatment), Day 56 (1 month after completing
AZLI treatment), Day 112 (3 months after completing AZLI treatment), and Day 196 (6 months after completing AZLI treatment).

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	04 October 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	Netherlands: 5
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 5

Country: Number of subjects enrolled	United States: 56
Worldwide total number of subjects	105
EEA total number of subjects	49

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)	24
Children (2-11 years)	65
Adolescents (12-17 years)	16
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 46 study sites in the United States and Europe. The first participant was screened on 04 October 2011. The last participant observation occurred on 29 May 2013.

Pre-assignment

Screening details:

109 participants were screened; 105 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 one 28-day course of Aztreonam for Inhalation Solution (AZLI), then were followed for a 24-week period (through Day 196). AZLI 75 mg was administered 3 times daily via the investigational eFlow® 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:

AZLI 75 mg administered 3 times daily via the investigational eFlow® nebulizer

Number of subjects in period 1	AZLI
Started	105
Completed	55
Not completed	50
Adverse event, non-fatal	2
Protocol-specified withdrawal criteria	45
Lost to follow-up	1
Withdrawal by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			
3 months to < 2 years	24	24	
≥ 2 years to < 6 years	25	25	
≥ 6 years to < 18 years	56	56	
Age continuous Units: years			
arithmetic mean	6.26		
standard deviation	± 4.743	-	
Gender categorical Units: Subjects			
Female	58	58	
Male	47	47	
Race Units: Subjects			
Asian	1	1	
Black or African Heritage	1	1	
White	99	99	
Other	2	2	
Not Permitted to be Recorded	2	2	
Ethnicity Units: Subjects			
Hispanic	5	5	
Not Hispanic	93	93	
Not Permitted to be Recorded	7	7	
Presence of Pseudomonas aeruginosa (PA)			
Of the 105 participants in the safety analysis set, 3 participants did not provide baseline samples (ie, oropharyngeal swab sample). All participants had a positive PA culture within 30 days of baseline.			
Units: Subjects			
Present at baseline	45	45	
Absent at baseline	57	57	
Did not provide samples at baseline	3	3	
Weight Units: kilogram(s)			
arithmetic mean	24.8		
standard deviation	± 15.69	-	
Height Units: cm			
arithmetic mean	113.9		
standard deviation	± 33.02	-	

BMI			
Units: kilogram(s)/square meter			
arithmetic mean	17.1		
standard deviation	± 2.57	-	

End points

End points reporting groups

Reporting group title	AZLI

Reporting group description:

Participants received one 28-day course of Aztreonam for Inhalation Solution (AZLI), then were followed for a 24-week period (through Day 196). AZLI 75 mg was administered 3 times daily via the investigational eFlow® nebulizer.

Subject analysis set title	Evaluable Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Evaluable Analysis Set consists of participants who completed study drug and did not receive an additional antipseudomonal antibiotic during the 28-day AZLI treatment course, and either completed the study through Day 196 with PA-negative cultures at every visit without the use of additional antipseudomonal antibiotics from Day 28 through Day 196 or had evidence of a positive PA-positive culture from Day 28 through Day 196.

Subject analysis set title	Sensitivity Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Sensitivity Analysis Set consists of participants who completed study drug and did not receive an additional antipseudomonal antibiotic during the 28-day AZLI treatment course, and either completed the study through Day 196 with PA-negative cultures at every visit without the use of additional antipseudomonal antibiotics from Day 28 through Day 196 or had evidence of a PA-positive culture from Day 28 through Day 196 or used any additional antipseudomonal antibiotics from Day 28 through Day 196.

Subject analysis set title	Sensitivity Analysis Set-Met Primary Efficacy Endpoint
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Sensitivity Analysis Set ≥ 6 years of age who met the primary efficacy endpoint with available data for this assessment were analyzed.

Subject analysis set title	Sensitivity Analysis Set-Didn't Meet Primary Efficacy Endpoint
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Sensitivity Analysis Set ≥ 6 years of age who did not meet the primary efficacy endpoint with available data for this assessment were analyzed.

Subject analysis set title	Full Analysis Set < 6 years of age with evaluable PK profiles
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Full Analysis Set < 6 years of age with evaluable PK profiles were analyzed.

Subject analysis set title	Full Analysis Set - no additional antipseudomonal antibiotic
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants from the Full Analysis Set who completed study drug and did not receive an additional antipseudomonal antibiotic during the 28-day AZLI treatment course were included in the analysis at all time points.

Primary: Percentage of Participants With PA-negative Cultures at All Time Points After Cessation of Active Treatment (Evaluable Analysis Set)

End point title	Percentage of Participants With PA-negative Cultures at All Time Points After Cessation of Active Treatment (Evaluable Analysis Set)[1]

End point description:

The percentage of participants with PA-negative cultures at all time points after cessation of active treatment at Day 28 (assessed at Days 56, 112, and 196) was summarized for the Evaluable Analysis Set.

End point type	Primary

End point timeframe:

Day 28 to Day 196

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	Evaluable Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: percentage of participants				
number (confidence interval 95%)	58.2 (47.4 to 69.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With PA-negative Cultures at All Time Points After Cessation of Active Treatment (Sensitivity Analysis Set)

End point title	Percentage of Participants With PA-negative Cultures at All Time Points After Cessation of Active Treatment (Sensitivity Analysis Set)[2]

End point description:

The percentage of participants with PA-negative cultures at all time points after cessation of active treatment at Day 28 (assessed at Days 56, 112, and 196) was summarized for the Sensitivity Analysis Set.

End point type	Primary

End point timeframe:

Day 28 to Day 196

Notes:

[2] - 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	Sensitivity Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: percentage of participants				
number (confidence interval 95%)	46.9 (37.1 to 56.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FEV1% Predicted

End point title	Change From Baseline in FEV1% Predicted

End point description:

Spirometry assessments were performed only in participants ≥ 6 years of age. Forced expiratory volume in 1 second (FEV1) % predicted was defined as FEV1 of the participant divided by the average FEV1 in the population for any person of similar age, sex and body composition.

End point type	Secondary

End point timeframe:

Baseline to Days 28, 56, 112, and 196

End point values	Sensitivity Analysis Set-Met Primary Efficacy Endpoint	Sensitivity Analysis Set-Didn't Meet Primary Efficacy Endpoint		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	27		
Units: percentage of FEV1% predicted				
arithmetic mean (standard deviation)				
Change at Day 28 (n=25 [met], 26 [did not meet])	-0.23 (± 10.373)	-0.38 (± 12.347)		
Change at Day 56 (n=25 [met], 26 [did not meet])	-0.2 (± 10.949)	-4.24 (± 7.513)		
Change at Day 112 (n=25 [met], 19 [did not meet])	0.32 (± 9.83)	-5.1 (± 7.948)		
Change at Day 196 (n=25 [met], 8 [did not meet])	-2.47 (± 8.895)	-8.85 (± 11.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CFQ-R RSS Score

End point title	Change From Baseline in CFQ-R RSS Score

End point description:

Respiratory symptoms (eg, coughing, congestion, wheezing) were assessed with the Cystic Fibrosis Questionnaire – Revised (CFQ-R) Respiratory Symptoms Scale (RSS) only in participants ≥ 6 years of age. The range of scores (units) is 0 to 100 with higher scores indicating fewer symptoms.

End point type	Secondary

End point timeframe:

Baseline to Days 28, 56, 112, and 196

End point values	Sensitivity Analysis Set-Met Primary Efficacy Endpoint	Sensitivity Analysis Set-Didn't Meet Primary Efficacy Endpoint		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	31		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Day 28 (n=24 [met], 29 [did not meet])	8.33 (± 15.883)	5.36 (± 8.937)		
Change at Day 56 (n=24 [met], 27 [did not meet])	6.37 (± 16.433)	6.17 (± 11.04)		
Change at Day 112 (n=24 [met], 21 [did not meet])	5.79 (± 14.397)	1.46 (± 14.636)		
Change at Day 196 (n=24 [met], 10 [did not meet])	6.13 (± 18.002)	5.83 (± 9.663)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PA-negative Cultures

End point title	Percentage of Participants With PA-negative Cultures
End point description:	
The percentage of participants with a PA-negative culture was summarized at each visit.	
End point type	Secondary
End point timeframe:	
Days 28, 56, 112, and 196	

End point values	Full Analysis Set - no additional antipseudomonal antibiotic			
Subject group type	Subject analysis set			
Number of subjects analysed	101			
Units: percentage of participants				
number (not applicable)				
Day 28	89.1			
Day 56	75.2			
Day 112	63.4			
Day 196	47.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Additional (Non-study) Antipseudomonal Antibiotics

End point title	Use of Additional (Non-study) Antipseudomonal Antibiotics

End point description:

The percentage of participants who used additional (non-study) antipseudomonal antibiotics (an indication of PA exacerbation) while on treatment and posttreatment was summarized.

End point type	Secondary

End point timeframe:

Baseline to Day 196

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	105			
Units: percentage of participants				
number (not applicable)				
On-treatment	1.9			
Posttreatment	43.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight

End point title	Change From Baseline in Weight

End point description:

End point type	Secondary

End point timeframe:

Baseline to Days 28, 56, 112, and 196

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	105			
Units: kilogram(s)				
arithmetic mean (standard deviation)				
Change at Day 28 (On-Treatment, n = 104)	0.3 (± 0.7)			
Change at Day 56 (Posttreatment, n = 101)	0.5 (± 0.72)			
Change at Day 112 (Posttreatment, n = 90)	0.8 (± 1.02)			
Change at Day 196 (Posttreatment, n = 69)	1.5 (± 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Height

End point title	Change From Baseline in Height

End point description:

End point type	Secondary

End point timeframe:

Baseline to Days 28, 56, 112, and 196

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	105			
Units: centimeter				
arithmetic mean (standard deviation)				
Change at Day 28 (On-Treatment, n = 104)	0.6 (± 0.87)			
Change at Day 56 (Posttreatment, n = 101)	1.4 (± 1.27)			
Change at Day 112 (Posttreatment, n = 90)	2.6 (± 2)			
Change at Day 196 (Posttreatment, n = 69)	4.5 (± 2.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI)

End point title	Change From Baseline in Body Mass Index (BMI)

End point description:

End point type	Secondary

End point timeframe:

Baseline to Days 28, 56, 112, and 196

End point values	AZLI			
Subject group type	Reporting group			
Number of subjects analysed	105			
Units: kg/m^2				
arithmetic mean (standard deviation)				
Change at Day 28 (On-Treatment, n = 104)	0.1 (± 0.57)			
Change at Day 56 (Posttreatment, n = 101)	0.1 (± 0.71)			
Change at Day 112 (Posttreatment, n = 90)	0 (± 0.97)			
Change at Day 196 (Posttreatment, n = 69)	0 (± 0.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Peak and Trough Plasma Concentrations of Aztreonam

End point title	Pharmacokinetics (PK) Peak and Trough Plasma Concentrations of Aztreonam

End point description:

The plasma concentration of aztreonam for participants < 6 years of age was obtained 1 hour after the first dose of AZLI on Day 1 and immediately prior to the last dose of AZLI on Day 28.

End point type	Secondary

End point timeframe:

Day 1 (1 hour postdose) and Day 28 (immediately prior to dosing)

End point values	Full Analysis Set < 6 years of age with evaluable PK profiles			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (1 hour postdose, n = 40)	578 (± 560)			
Day 28 (immediately prior to dosing, n = 43)	125 (± 166.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to Day 28 plus 30 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	AZLI

Reporting group description:

Participants received one 28-day course of Aztreonam for Inhalation Solution (AZLI), then were followed for a 24-week period (through Day 196). AZLI 75 mg was administered 3 times daily via the investigational eFlow® nebulizer.

Serious adverse events	AZLI		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 105 (7.62%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Pseudomonas test positive			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitus acute			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infectious mononucleosis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonas infection			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
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	66 / 105 (62.86%)		
Investigations			
Pseudomonas test positive			
subjects affected / exposed	20 / 105 (19.05%)		
occurrences (all)	20		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 105 (14.29%)		
occurrences (all)	15		

Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 7 / 105 (6.67%) 8 7 / 105 (6.67%) 7		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 42 / 105 (40.00%) 51 10 / 105 (9.52%) 11		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	 8 / 105 (7.62%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2012	Increased enrollment from approximately 80 subjects to approximately 105 subjects to meet the PIP commitment of 60 subjects evaluable for the primary endpoint and clarified enrollment of 10 subjects evaluable for the primary endpoint in each age subset throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported