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 number2011-001362-18Trial protocolDE ES FR IT Outside EU/EEAGlobal end of trial date03 April 2013Results informationResult version numberv1 (current)This version publication date22 March 2016First version publication date05 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?	Νο		
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	
N = +		

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	I taly: 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

0

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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

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			

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
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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)		

No statistical analyses for this end point

Secondary: Change From Baseline in CFQ-R Respiratory Symptoms Scale (RSS) Score in Subjects Aged \geq 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.

Participants of years of age were analyzed.		
End point type	Secondary	
End point timeframe:		
3aseline 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

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	57.4		
antibiotics			

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 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

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

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.	

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 exact statistics.	cerbation was summarized using Kaplan-Meier (KM) summary				
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		

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. A ways or as from the lawestigater's assessment for subjects of 6 years

treatment for subjects	o years of as if	on 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 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 timeframe	End point type	Secondary
end point unerane.	End point timeframe:	
Baseline to Day 168	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		

No statistical analyses for this end point

Adverse events information				
Timeframe for reporting adverse events	S:			
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		
	1		
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		
Needloopgestign			
subjects affected (exposed			
	12/61 (19.67%)		
occurrences (all)	16		
Oropharyngeal pain			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
	0		
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			
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subjects affected / exposed	5 / 61 (8.20%)	
occurrences (all)	5	
Rhinorrhoea		
subjects affected / exposed	10 / 61 (16.39%)	
occurrences (all)	15	
Rhonchi		
subjects affected / exposed	6 / 61 (9.84%)	
occurrences (all)	7	
Sputum Increased		
subjects affected / exposed	9 / 61 (14.75%)	
occurrences (all)	12	
Wheezing		
subjects affected / exposed		
	9 / 61 (14.75%)	
occurrences (all)	12	
Infections and infestations		
Rhinitis		
subjects affected / exposed	10 / 61 (16.39%)	
occurrences (all)	11	
Metabolism and nutrition disorders		
Decreased appetite		
subjects affected / exposed	5 / 61 (8.20%)	
occurrences (all)	6	

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