Clinical trial results:
Randomized, Double-Blind, Phase 3B Trial to Evaluate the Safety and Efficacy of 2 Treatment Regimens of Aztreonam 75 mg Powder and Solvent for Nebulizer Solution / Aztreonam for Inhalation Solution (AZLI) in Pediatric Subjects with Cystic Fibrosis (CF) and New Onset Respiratory Tract Pseudomonas aeruginosa (PA) Infection/Colonization

Summary

EudraCT number	2016-002749-42
Trial protocol	BE GB IE AT FR DE ES NL IT GR DK Outside EU/EEA
Global end of trial date	23 September 2021

Results information

Result version number	v1 (current)
This version publication date	18 March 2022
First version publication date	18 March 2022

Trial information

Trial identification

Sponsor protocol code	GS-US-205-1850

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03219164
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	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@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	23 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2020
Global end of trial reached?	Yes
Global end of trial date	23 September 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and efficacy of a 14-day course versus a 28-day course of aztreonam for inhalation solution (AZLI) in pediatric participants with new onset Pseudomonas aeruginosa respiratory tract infection or colonization.

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	28 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	26 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	149
EEA total number of subjects	76

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)	30
Children (2-11 years)	85
Adolescents (12-17 years)	34
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 study sites in Europe, Israel, and the United States. The first participant was screened on 28 November 2017. The last study visit occurred on 23 September 2021.

Pre-assignment

Screening details:

149 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	AZLI 14 Days + Placebo 14 Days

Arm description:

75 milligrams per milliliter (mg/ml) of aztreonam was administered thrice daily (TID) for 14 days followed by placebo to match (PTM) aztreonam TID for 14 days, both aztreonam and PTM aztreonam were delivered via the PARI Altera® Nebulizer System. Participants below 2 years received aztreonam for inhalation solution (AZLI) and PTM aztreonam via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.

Arm type	Experimental
Investigational medicinal product name	AZLI
Investigational medicinal product code	
Other name	Cayston®, Aztreonam
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

75 mg/ml administered thrice daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Administered thrice daily.

Arm title	AZLI 28 Days

Arm description:

75 mg/ml of aztreonam was administered TID for 28 days via the PARI Altera® Nebulizer System. Participants below 2 years received AZLI via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.

Arm type	Experimental
Investigational medicinal product name	AZLI
Investigational medicinal product code	
Other name	Cayston®, Aztreonam
Pharmaceutical forms	Powder and solvent for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:
75 mg/ml administered thrice daily.

Number of subjects in period 1	AZLI 14 Days + Placebo 14 Days	AZLI 28 Days
Started	74	75
Completed	49	57
Not completed	25	18
Non-Compliance with Study Drug	1	-
Withdrew Consent by Parent/Guardian	5	4
Protocol violation	-	1
Adverse event	1	-
Study Terminated by Sponsor	16	12
Lost to follow-up	1	1
Withdrew Assent	1	-

Baseline characteristics

Reporting groups	
Reporting group title	AZLI 14 Days + Placebo 14 Days
Reporting group description:	
75 milligrams per milliliter (mg/ml) of aztreonam was administered thrice daily (TID) for 14 days followed by placebo to match (PTM) aztreonam TID for 14 days, both aztreonam and PTM aztreonam were delivered via the PARI Altera® Nebulizer System. Participants below 2 years received aztreonam for inhalation solution (AZLI) and PTM aztreonam via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.	
Reporting group title	AZLI 28 Days
Reporting group description:	
75 mg/ml of aztreonam was administered TID for 28 days via the PARI Altera® Nebulizer System. Participants below 2 years received AZLI via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.	

Reporting group values	AZLI 14 Days + Placebo 14 Days	AZLI 28 Days	Total
Number of subjects	74	75	149
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	7.3	6.5	
standard deviation	± 5.34	± 4.91	-
Gender categorical Units: Subjects			
Female	35	33	68
Male	39	42	81
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	1	1	2
Black or African American	1	0	1
White	69	73	142
Other	2	1	3
Ethnicity			
Not Permitted = collection of ethnicity information not allowed by local regulations.			
Units: Subjects			
Not Hispanic or Latino	66	65	131
Hispanic or Latino	8	9	17
Not Permitted	0	1	1

End points

End points reporting groups

Reporting group title	AZLI 14 Days + Placebo 14 Days

Reporting group description:

75 milligrams per milliliter (mg/ml) of aztreonam was administered thrice daily (TID) for 14 days followed by placebo to match (PTM) aztreonam TID for 14 days, both aztreonam and PTM aztreonam were delivered via the PARI Altera® Nebulizer System. Participants below 2 years received aztreonam for inhalation solution (AZLI) and PTM aztreonam via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.

Reporting group title	AZLI 28 Days

Reporting group description:

75 mg/ml of aztreonam was administered TID for 28 days via the PARI Altera® Nebulizer System. Participants below 2 years received AZLI via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.

Subject analysis set title	Tobramycin Nebulizer Solution (TNS)
Subject analysis set type	Full analysis

Subject analysis set description:

The TNS group included historical data for the percentage of participants with PA-negative cultures during 28 days post-treatment period pooled from the published results from the studies conducted on the participants with new onset of PA infection and similar TNS treatment duration and follow-up.

Primary: Percentage of Participants With Pseudomonas aeruginosa (PA)-negative Cultures Through 28 Days Post-Treatment in the 14-Day Treatment Group vs 28-Day Treatment Group

End point title	Percentage of Participants With Pseudomonas aeruginosa (PA)-negative Cultures Through 28 Days Post-Treatment in the 14-Day Treatment Group vs 28-Day Treatment Group

End point description:

Evaluable Analysis Set included participants who completed study drug with at least 75% compliance, did not use any anti-PA antibiotics while on study treatment with AZLI.

End point type	Primary

End point timeframe:

28 days post treatment (Weeks 4 to 6 for the 14 Day treatment group and Weeks 4 to 8 for the 28 Day treatment group)

End point values	AZLI 14 Days + Placebo 14 Days	AZLI 28 Days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	71		
Units: percentage of participants				
number (confidence interval 95%)	55.9 (43.3 to 67.9)	63.4 (51.1 to 74.5)		

Statistical analyses

Statistical analysis title	AZLI 14 Days + Placebo 14 Days vs AZLI 28 Days
Comparison groups	AZLI 14 Days + Placebo 14 Days v AZLI 28 Days

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in percentage
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.6
upper limit	8.6

Notes:

[1] - Non-inferiority of the 14-day treatment regimen was claimed if the lower bound of 1-sided 97.5% confidence limit of the treatment difference (14-day course group vs 28-day course group) was above the noninferiority margin of -20%.

Secondary: Time From Primary Eradication to PA Recurrence Over a 108-Week Post-Treatment Follow-up Period

End point title	Time From Primary Eradication to PA Recurrence Over a 108-Week Post-Treatment Follow-up Period

End point description:

The primary eradication was achieved when all cultures through 28 days post AZLI treatment were PA negative. Recurrence after PA eradication was defined as first positive PA culture result in participant who successfully met primary endpoint and had no PA-positive culture from local lab at Week 4 through Week 6 for AZLI 14 Days group or through Week 8 for AZLI 28 Days group. Participants in the Evaluable Analysis Set were analyzed. 9999=Not Available as the calculated percentiles of event rate were not reached.

End point type	Secondary

End point timeframe:

Last dose date of AZLI up to Week 112

End point values	AZLI 14 Days + Placebo 14 Days	AZLI 28 Days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	71		
Units: months				
median (inter-quartile range (Q1-Q3))	19.3 (10.5 to 9999)	9999 (4.9 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PA Recurrence for a Sub-Group of Participants Matching the Population in the TNS ELITE Study Over a 108-Week Post-Treatment Follow-up Period

End point title	Time to PA Recurrence for a Sub-Group of Participants Matching the Population in the TNS ELITE Study Over a 108-Week Post-Treatment Follow-up Period

End point description:

ELITE study (NCT00391976): Participants with CF who had early PA infection received TNS. ELITE Study

Matching Analysis Set=Participants from Evaluable Analysis set who satisfied published criteria for efficacy analysis population:
- Participants must be ≥ 6 months at randomization, no history of positive (+) anti-PA antibody (no anti-PA IgG antibody interpretation at Screening/Baseline) on record
- Did not use anti-pseudomonal antibiotics and PA negative (-) through 28 days after completion of treatment, within 2 years of Screening
- Non-missing PA culture result at 28 days after AZLI last dose
- No protocol deviation from study drug administration compliance and documented new onset of + respiratory tract culture for PA within 30 days of Screening [as either first lifetime documented PA+ culture/PA recovered after at least a 2-year history of PA- respiratory cultures (at least 2 cultures/year)]
9999=Not Available as the calculated percentiles of event rate were not reached.

End point type	Secondary

End point timeframe:

Last dose date of AZLI up to Week 112

End point values	AZLI 14 Days + Placebo 14 Days	AZLI 28 Days		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: months				
median (inter-quartile range (Q1-Q3))	19.3 (10.5 to 9999)	15.2 (4.7 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PA-negative Cultures Through 28 Days Post-Treatment in the 14-Day Treatment Group vs Historical Pooled Data for PA Eradication at 28 Days Post-Treatment in Participants Treated With Tobramycin Nebulizer Solution (TNS)

End point title	Percentage of Participants With PA-negative Cultures Through 28 Days Post-Treatment in the 14-Day Treatment Group vs Historical Pooled Data for PA Eradication at 28 Days Post-Treatment in Participants Treated With Tobramycin Nebulizer Solution (TNS)[2]

End point description:

The historical data for the percentage of participants with PA-negative cultures during 28 days post-treatment period was pooled from the published results from the studies conducted on the participants with new onset of PA infection and similar TNS treatment duration and follow-up. AZLI 14 Day treatment group: Evaluable Analysis Set; TNS group: Participants with PA-negative cultures during 28 days post-treatment period whose historical data were pooled from published results from studies conducted on the participants with new onset of PA infection and similar TNS treatment duration and follow-up.

End point type	Secondary

End point timeframe:

28 days post treatment (Weeks 4 to 6 for the 14 Day treatment group)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was reported for AZLI 14 Day group and for the TNS group historical data pooled from the published results from the studies conducted on the participants with new onset of PA infection and similar TNS treatment duration and follow-up was reported.

End point values	AZLI 14 Days + Placebo 14 Days	Tobramycin Nebulizer Solution (TNS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	31		
Units: percentage of participants				
number (not applicable)	55.9	77.0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: First dose date up to 28 days plus 30 days;
All-Cause Mortality: Randomization up to 112 weeks

Adverse event reporting additional description:

Adverse Events: Safety Analysis Set included participants who were randomized and received at least one dose of study drug.
All-Cause Mortality: Intent-To-Treat Analysis Set included all participants who were randomized in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	AZLI 14 Days Placebo 14 Days

Reporting group description:

75 mg/ml of aztreonam was administered TID for 14 days followed by PTM aztreonam TID for 14 days, both aztreonam and PTM aztreonam were delivered via the PARI Altera® Nebulizer System. Participants below 2 years received AZLI and PTM aztreonam via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.

Reporting group title	AZLI 28 Days

Reporting group description:

75 mg/ml of aztreonam was administered TID for 28 days via the PARI Altera® Nebulizer System. Participants below 2 years received AZLI via the SmartMask® Baby, 2 to below 6 years via the SmartMask Kids® and above 6 years via the nebulizer mouthpiece.

Serious adverse events	AZLI 14 Days Placebo 14 Days	AZLI 28 Days	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 74 (6.76%)	4 / 75 (5.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Pseudomonas test positive			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pseudomonas infection			
subjects affected / exposed	1 / 74 (1.35%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AZLI 14 Days Placebo 14 Days	AZLI 28 Days	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 74 (37.84%)	22 / 75 (29.33%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 74 (5.41%)	6 / 75 (8.00%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 74 (6.76%)	1 / 75 (1.33%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 74 (16.22%)	11 / 75 (14.67%)	
occurrences (all)	13	15	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 74 (5.41%)	3 / 75 (4.00%)	
occurrences (all)	4	3	
Influenza			
subjects affected / exposed	1 / 74 (1.35%)	5 / 75 (6.67%)	
occurrences (all)	1	5	
Rhinitis			
subjects affected / exposed	5 / 74 (6.76%)	0 / 75 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2017	• All computed tomography (CT) scan assessments were removed • Exploratory objectives and endpoints related to CT scans were removed • Clarified that all retreatment options listed in the protocol were non-exclusive • Clarified that spirometry was only to be performed on participants who can reliably perform spirometry assessments • Clarified that clinical observation should also be performed pre-and poststudy drug administration for participants 6 years of age and older who can't reliably perform spirometry assessments • Removed collection of body weight, height and vital signs after baseline, with the exception of unscheduled visits • Removed all nasal swabs assessments after Day 1 • Eligibility criteria clarified as needed • Corrected the follow-up culture phase schedule to specify that the first visit will occur at Week 16 and then every twelve weeks after that • Removed hematology and serum chemistry samples from Baseline (if results are available within the last 12 months) and from the follow-up culture phase • Clarified that participants must switch IP kits at Day 15.
06 November 2017	• The number of study centres were increased from 75 to 85 to mitigate risk of slow recruitment • Exclusion criterion was amended so that antibiotics such as azithromycin were allowable in 7 days prior to Screening • Respiratory sample collection methods expanded • Biomarker sections updated to allow PA-specific antibody titre blood draw to be avoided if results were available within 24 months • Change made to prohibited concomitant medication section to clarify that concurrent use of oral antipseudomonal antibiotics for a respiratory event was prohibited from Screening to Day 28 • Spirometry sections updated to clarify that percentage of forced expiratory volume (FEV1%) predicted was reported at all visits and was calculated by site • Clarification throughout study procedure section as to what types of AEs/SAEs were reported at each visit • Medical History section updated to clarify that the participant`s PA infection history, including the number of previous PA infections, number of cultures taken and sampling methods in the previous 2 years were also recorded.
15 April 2020	• Clarification on how the missing PA culture data was evaluated • Documentation of which personnel wiould be blinded/unblinded throughout the study • Clarification that 130 evaluable participants were required for the efficacy analyses • Unblinding of Gilead personnel was required for the primary analysis • Confirmed that respiratory samples collected outside of the study as standard of care may be sent to local laboratory • Local lab culture data may be used for analysis purposes • The Biofire testing panel would be used for microbiological assessment of the nasal swabs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 September 2021	During ongoing Coronavirus disease 2019 (COVID-19) pandemic, the risk of continuing the trial in this vulnerable CF pediatric participant population considerably outweighed the benefits of trial continuation. Therefore, the study was terminated early and at the time of study termination, all evaluable participants completed the initial eradication period and provided data for the primary analysis; more than 60% of participants evaluable for the primary analysis also completed 108weeks followup period, in line with the terms of the agreed pediatric investigational plan (PIP) for Cayston approved by the Pediatric Committee (PDCO) of the European Medicines Agency (EMA). Throughout the COVID-19 pandemic, exceptional measures were adopted where necessary to mitigate the impact to the conduct of the trial. These measures included: on site participant visits rearranged into remote visits, on site participant visits performed however without all per protocol required study procedures, remote site close out visits and etc. Expected periodic reports detailing all exceptional measures were submitted to applicable National Regulatory Authorities in EU countries where required.	-

Notes:

Limitations and caveats

None reported