24 September 2015
EMA/679984/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cayston

International non-proprietary name: aztreonam

Procedure No. EMEA/H/C/000996/P46 034

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 10 July 21015, the MAH submitted a final clinical study report for Study GS-US-205-0170, '*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*' in accordance with Article 46 of Regulation (EC) No. 1901/2006.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The following study has been provided: *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*'.

2.2. Information on the pharmaceutical formulation used in the study

Not applicable

2.3. Clinical aspects

2.3.1. Introduction

Cystic fibrosis (CF) is characterized by defective ion transport across the respiratory epithelium, leading to secretion of abnormally viscous mucus that interferes with the mucociliary transport mechanism normally responsible for clearance of bacteria, other organisms, and debris from the airways. CF patients thus become particularly susceptible to pulmonary infections with organisms including Pseudomonas aeruginosa (PA), Burkholderia cepacia, and Stenotrophomonas maltophilia. PA is the most significant bacterial pathogen associated with CF pulmonary disease, it is associated with higher rates of pulmonary function decline, and is a significant predictor of mortality. Infected patients experience progressive obstruction of the airways and loss of lung function, which is due in large part to the inflammatory response to chronic bacterial infection. Patients infected with PA experience episodes of acute pulmonary exacerbation, characterized by worsening respiratory symptoms and acute decline in lung function.

Aztreonam 75 mg powder and solvent for nebuliser solution (Cayston®; AZLI) initially received a conditional marketing authorization in the European Union (EU) on 21 September 2009 for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa (PA) in patients with cystic fibrosis (CF) aged 18 years and older. On 23 June 2011, the Committee for Medicinal Products for Human Use (CHMP) endorsed the conversion of the conditional marketing authorization to a marketing authorization not subject to specific obligations, which was subsequently approved by the European Commission on 05 September 2011. A Type II Variation to extend the Cayston indication to include pediatric CF patients with chronic PA infection aged 6 years and older was approved by the European Commission on 23 July 2012. This submission presents the safety and efficacy of continuous alternating therapy (CAT) with AZLI and tobramycin inhalation solution (TIS) in pediatric subjects aged 8 years and older, treated in Phase 3 Study GS-

US-205-0170. The primary objective of this study was to evaluate the safety and efficacy of a continuous alternating therapy (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.

2.3.2. Clinical study

Description

Study GS-US-205-0170 is a Phase 3, randomized, double-blind, placebo-controlled, multicentre study evaluating 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. This study was conducted at 45 sites that enrolled subjects (of 73 total activated sites), all located in the United Stated (US). The study start date was 13 December 2012 (first subject consented) and Study end date was 15 January 2015 (last subject visit). The study report date is 26 May 2015.

Methods

Objective(s)

The primary objective of this study was to evaluate the safety and efficacy of a CAT regimen with AZLI and tobramycin inhalation solution (TIS) in adult and paediatric subjects with cystic fibrosis (CF) and pulmonary Pseudomonas aeruginosa (PA) infection. No secondary objectives were planned for this study.

Study design

This study was a randomized, double-blind, placebo-controlled, multicenter trial that included an initial 4-week TIS run-in phase followed by a 24-week comparative treatment phase. The duration of the study period was up to 30 weeks and involved up to 9 visits (Screening Visit 1 and Enrollment Visit 2 were allowed to be combined provided the subject met all required entry criteria). Enrolled subjects received 28 days of open-label TIS during the run-in phase. Subjects who continued to be eligible for the study were randomized with a 1:1 allocation to receive one of the following treatments:

- Treatment 1: Three 28-day cycles of double-blind AZLI 75 mg given 3 times daily, alternating with 28-day cycles of open-label TIS 300 mg given twice daily
- Treatment 2: Three 28-day cycles of double-blind placebo given 3 times daily, alternating with 28-day cycles of open-label TIS 300 mg given twice daily

Eligible subjects were stratified by disease severity (forced expiratory volume in the first second [FEV1] ≤ 50% or > 50% predicted at Day 1) and the number of acute respiratory exacerbations requiring hospitalization or intravenous (IV) antibiotic use (1, 2, or ≥ 3) as determined by the investigator, in the 12 months prior to screening, plus any that occurred between screening and enrollment.

Study population /Sample size

Study population

Male or female subjects at least 6 years of age with confirmed CF and documented chronic pulmonary PA infection and an FEV1 of ≥ 25% and ≤ 75% predicted. Subjects were required to have been hospitalized at least once or have had at least 1 course of IV antibiotics for an acute respiratory exacerbation within the previous 12 months prior to screening. Subjects were clinically stable with no evidence of significant respiratory symptoms or findings on available chest

radiograph at screening or enrollment that would require administration of IV antibiotics, oxygen supplementation, or hospitalization.

Sample size
With 125 subjects per treatment group there is at least 85% power at a 2-sided 5% significance level to declare superiority of alternating TIS/AZLI to TIS/Placebo in the rate of protocol-defined pulmonary exacerbations assuming a dispersion parameter of k=0.267 and a 6-month exacerbation rate of 1.15 for TIS/Placebo and 0.70 for TIS/AZLI (approximately a 40% reduction in exacerbation rate). Assumptions used in the sample size calculation are based on results observed from the GS-US-205-0110 study for subjects receiving AZLI 75 mg TID and TIS 300 mg BID.

Treatments
Treatment 1: Three 28-day cycles of double-blind AZLI 75 mg given 3 times daily, alternating with 28-day cycles of open-label TIS 300 mg given twice daily
Treatment 2: Three 28-day cycles of double-blind placebo given 3 times daily, alternating with 28-day cycles of open-label TIS 300 mg given twice daily

Outcomes/endpoints
Efficacy:
The primary efficacy endpoint was the rate of **protocol-defined pulmonary exacerbations** (PDEs) from Day 1 through Week 24. Events that met the definition of PDE 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 were verified by a blinded independent adjudication committee. The adjudication committee also determined discrete exacerbation events to account for multiple antibiotics prescribed for each exacerbation.

Secondary efficacy endpoints were the following:
- Average actual change from baseline in FEV1 % predicted at the end of each course of study drug (Weeks 4, 12, and 20)
- Percent of subjects who used nonstudy IV or inhaled antibiotics for PDEs, Day 1 to Week 24
- Time to first PDE
- Rate of hospitalizations for a respiratory event
- Average change from baseline in the Cystic Fibrosis Questionnaire- Revised (CFQ-R) Respiratory Symptom Scale (RSS) score at the end of each course of study drug (Weeks 4, 12, and 20)

Numerous exploratory efficacy endpoints were defined, including change from baseline in pulmonary function tests, individual CFR-Q domains, EQ-5D utility index score and VAS, CFRSD-CRISS weekly average score, BMI, and weight. Additional exploratory endpoints were respiratory hospitalizations (percent of subjects with respiratory hospitalizations, number and percent of days hospitalized due to respiratory events, and time to first respiratory hospitalization); use of non-study antibiotics for PDEs; and missed school/work days.

Microbiology endpoints of interest were:
- Change from baseline in sputum PA density at each study visit
- Presence or absence of other respiratory pathogens (Staphylococcus aureus [methicillin-resistant (MRSA) or methicillin-sensitive (MSSA)], Burkholderia species [spp], Stenotrophomonas maltophilia, Achromobacter spp, Aspergillus spp) at each study visit
- Change in minimum inhibitory concentration (MIC) of aztreonam and of tobramycin for PA at each study visit
- Change in MIC of other antibiotics for PA at each study visit

Pharmacokinetics: There were no pharmacokinetic analyses planned or performed for this study.
Safety: Safety assessments included monitoring for adverse events (AEs), deaths, and pregnancies; clinical laboratory evaluations; body weight and vital sign measurements; airway

reactivity (percent change in FEV1 [L] at 30 minutes post-treatment from the pre-treatment measure at that visit); and nonstudy drug use.

Statistical Methods

Demographics and Baseline Characteristics: Subject demographic data and baseline characteristics were summarized by treatment group and overall using descriptive statistics (sample size, mean, standard deviation, median, quartile 1 [Q1], quartile 3 [Q3], minimum, and maximum) for continuous data and by the number and percent of subjects for categorical data. Summaries of demographic data and baseline characteristics were provided for the run-in and comparative safety analysis sets. For categorical demographic and baseline characteristics, the Fisher exact test was used to compare treatment arms. For continuous demographic and baseline characteristics, the Wilcoxon rank-sum test was used to compare treatment arms.

Efficacy and Microbiology: The primary analysis was conducted using the intent-to-treat (ITT) Analysis Set to test the null hypothesis of no difference between AZLI and placebo in the rate of PDE. The primary endpoint was analyzed using a negative binomial regression method with an offset parameter to account for follow-up time and was tested at the 2-sided 0.05 level.

Sensitivity analyses of the primary endpoint were performed using a Wilcoxon rank-sum test and a Poisson regression model. A time-to-multiple PDE analysis was performed using the Andersen-Gill formulation of the Cox proportional hazard model. Additional sensitivity analyses were performed using the Per Protocol (PP) Analysis Set as well as a modified definition of PDE. The PP Analysis Set included subjects in the ITT Analysis Set who had documented evidence of CF diagnosis, used no other investigational drug or device, received no AZLI within 28 days prior to randomization, and had a relative treatment compliance of at least 50% while on study and received at least 14 days of study treatment.

The primary efficacy endpoint and associated sensitivity analyses were summarized for the ITT Analysis Set in several subgroups, including sex (male versus female), disease severity (FEV1 > 50% predicted, FEV1 $\leq$ 50% predicted) , age (< 18 years, $\geq$ 18 years; 6 to 12 years, 13 to 17 years), previous exacerbations (1, 2, and $\geq$ 3), and azithromycin use (yes, no).

All secondary endpoints were based on analyses of the comparative phase (Day 1 through Week 24) and were based on the ITT Analysis Set. Average changes from baseline in FEV1 % predicted and CFQ-R RSS score at the end of each course of blinded study drug (AZLI/placebo) were analyzed using a mixed effect model repeated measures (MMRM) method. The models included terms for baseline value, previous exacerbations (1, 2, $\geq$ 3), treatment, visit, and treatment-by-visit interaction.

The percent of subjects who used nonstudy IV or inhaled antibiotics for PDEs, Day 1 through Week 24, were analyzed using the Fisher exact test. Survival analyses for the time to first PDE were summarized using Kaplan-Meier (KM) summary statistics and analyzed using the log-rank test. The rate (per subject) of hospitalizations for a respiratory event was analyzed using negative binomial regression.

The exploratory efficacy analyses were performed on the ITT Analysis Set. Changes in pulmonary function tests (FEV1, FEV1 % predicted, FVC, and FEF25-75), patient-reported outcomes (CFQ-R, CFRSD, and EQ-5D), sputum PA density, weight, and BMI were analysed using MMRM models that included changes from baseline at all postbaseline visits through Week 24.

Microbiology analyses included the proportion of subjects with PA considered resistant to each antibiotic tested, as well as beta-lactam resistant and multidrug-resistant PA, and were summarized by treatment group at each study visit.

The 50% and 90% minimum inhibitory concentration (MIC50 and MIC90) of aztreonam, tobramycin, and other antibiotics (amikacin, cefepime, ceftazidime, ciprofloxacin, piperacillin, piperacillin/tazobactam, meropenem, ticarcillin/clavulanate) for all PA isolates and for the PA isolate with the highest MIC (µg mL-1) from each subject at each visit were summarized as well as geometric mean, number of isolates, minimum, maximum).

Change (increased, unchanged, or decreased) from baseline in aztreonam MIC and in tobramycin MIC, as well as other antibiotic MICs, at each postbaseline visit through Week 24 for the PA isolate with the highest respective MIC at baseline from each subject were summarized. The Cochran-Mantel-Haenszel (CMH) test (row mean scores) was used to analyze the categorized change. The number and percent of subjects with a PA isolate identified as having the highest aztreonam MIC at baseline that was not detected postbaseline was also summarized for each visit. The number and percent of subjects with a PA isolate identified as having the highest tobramycin MIC at baseline that was not detected postbaseline was also summarized for each visit.

The number and percentage of subjects with each respiratory pathogen were summarized at Day -28, baseline (Day 1), and each postbaseline visit through Week 24. The number of subjects with a respiratory pathogen present or absent at any postbaseline visit (Day 1 through Week 24) were also summarized for each respiratory pathogen.

Safety: Safety data were summarized using descriptive statistics based on either the TIS Run-in Safety Analysis Set or the Comparative Phase Safety Analysis Set. Note that in general, AEs presented in this report were either TIS run-in emergent or comparative-phase treatment emergent. Laboratory abnormalities were treatment emergent. These are referred to as TIS run-in-emergent AEs or comparative phase AEs and laboratory abnormalities; AEs that were not treatment emergent are identified as such.

CHMP comment:
The only objective of this study was to evaluate the safety and efficacy of a continuous alternating therapy regimen in adult and paediatric subjects with cystic fibrosis and pulmonary *Pseudomonas aeruginosa* infection. The single primary endpoint allows for an adequate analysis.
In SAP a conservative analysis is proposed (binominal regression) to test the null hypothesis of no difference between AZLI and placebo.

Results

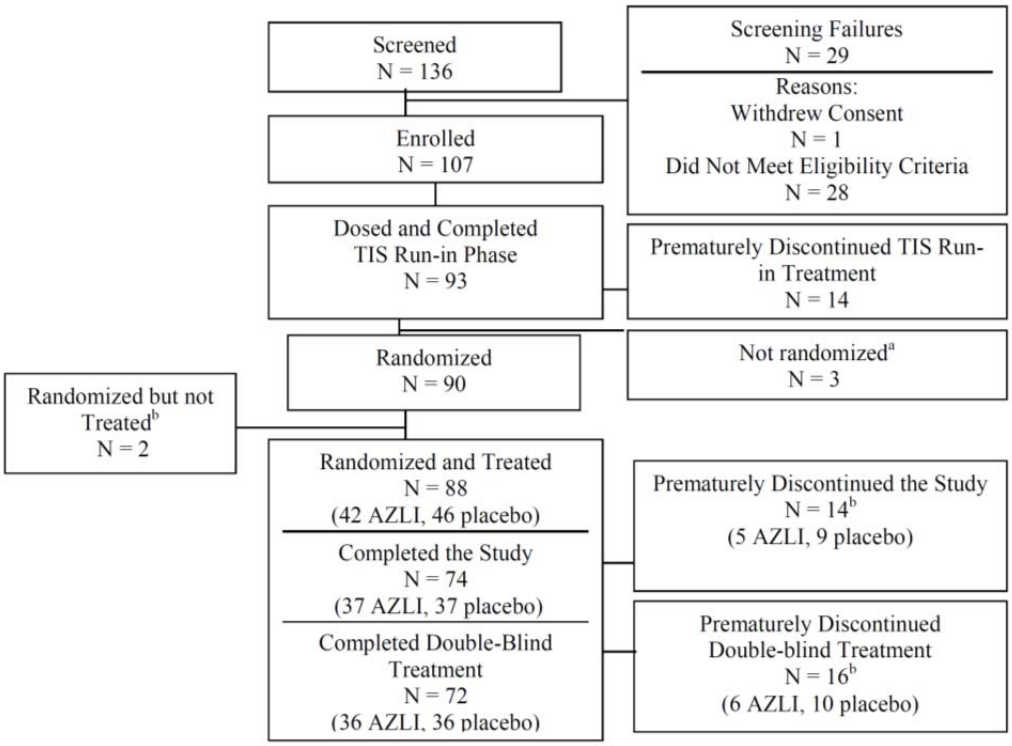
Recruitment / Number analysed

The planned sample size for this study was 250 subjects, 125 subjects per treatment group.

During the enrolment period, 73 sites were activated, only 45 of which enrolled subjects. The study was ultimately closed to enrolment early because projections based on repeated feasibility surveys with the sites indicated the enrolment goals would not be reached. Enrolment was substantially hampered due to 1) competing CF trials and 2) the increasing use of CAT treatment as standard care for CF patients during the enrolment period, which resulted in patients being unwilling to enrol in a randomized, placebo-controlled trial. Of the 107 subjects enrolled, 93 subjects completed TIS run-in treatment, and a total of 90 subjects (43 in the AZLI group and 47 in the placebo group) were randomized. As a consequence, this study was underpowered.

A total of 88 subjects (42 in the AZLI group and 46 in the placebo group) received at least 1 dose of double-blind study treatment. Thirty-six subjects in each treatment group completed double-blind study treatment.

Figure 1. GS-US-205-0170: Overview of Disposition of Study Subjects



Assessor's comment: Enrolment did not meet the planned sample size of 125 subjects per treatment group. In total 107 subjects were enrolled of whom 72 completed the double blind treatment period, 36 subjects per treatment group.

Baseline data

The baseline age of subjects in the TIS Run-in Safety Analysis Set (Day -28) ranged from 8.0 years to 68.0 years, with a mean age of 28.0 years. A majority of these 107 subjects (82.2%, 88 subjects) were 18 years of age or older. Demographic characteristics (Day 1) of subjects in the Comparative Safety Analysis Set (42 subjects in the AZLI group and 46 subjects in the placebo group) were generally similar to those of the TIS Run-in Safety Analysis Set and were similar between treatment groups. Based on analysis of the ITT Analysis Set (all subjects randomized), demographics were similar to those for the Comparative Safety Analysis Set, and no statistically significant differences between the AZLI and placebo treatment groups were observed for the ITT Analysis Set.

Table 1. GS-US-205-0170: Demographic Characteristics (comparative safety analysis set)

	AZLI 75 mg TID (N=42)	Placebo (N=46)	Total (N=88)	P-value[a]
Age (years) at Day 1				
N	42	46	88	0.96
Mean (SD)	28.5 (12.09)	28.3 (10.80)	28.4 (11.37)	
Median	25.5	26.0	26.0	
Q1, Q3	21.0, 35.0	21.0, 36.0	21.0, 35.5	
Min, Max	10.0, 68.0	8.0, 56.0	8.0, 68.0	
Age Group at Day 1				
6 to 12 years	3 (7.1%)	1 (2.2%)	4 (4.5%)	0.61
13 to 17 years	5 (11.9%)	5 (10.9%)	10 (11.4%)	
< 18 years	8 (19.0%)	6 (13.0%)	14 (15.9%)	0.56
≥ 18 years	34 (81.0%)	40 (87.0%)	74 (84.1%)	
Gender				
Male	18 (42.9%)	19 (41.3%)	37 (42.0%)	1.00
Female	24 (57.1%)	27 (58.7%)	51 (58.0%)	
Race				
American Indian or Alaska Native	0	1 (2.2%)	1 (1.1%)	0.79
White	40 (95.2%)	44 (95.7%)	84 (95.5%)	
Other	2 (4.8%)	1 (2.2%)	3 (3.4%)	
Ethnicity				
Hispanic or Latino	5 (11.9%)	4 (8.7%)	9 (10.2%)	0.73
Not Hispanic or Latino	37 (88.1%)	42 (91.3%)	79 (89.8%)	

a P-values are from a two-sided Fisher exact test for categorical variables and a Wilcoxon rank-sum test for continuous variables.

CHMP comment:
The study enrolled relatively few paediatric patients (n=19, 18%), and only 14 paediatric patients were included in the comparative phase.

Baseline Disease Characteristics

At TIS run-in phase baseline (Day -28), mean (SD) BMI was 21.35 (3.844) kg/m2 for subjects in the TIS Run-in Safety Analysis Set. Mean (SD) FEV1 % predicted was 51.72 (15.580). Mean (SD) baseline CFQ-R RSS was 63.35 (17.410). Overall, 84 of 107 subjects (78.5%) had used an inhaled antibiotic for maintenance therapy during the 12 months prior to enrollment in the study. For 99 subjects (95.2%), PA was present at Day -28 and/or at the screening visit. Mean (SD) log10 PA colony-forming units per gram (CFU/g) for subjects with PA present at Day -28 was 6.53 (1.047), and the MIC50 and MIC90 of aztreonam for all PA isolates (150 isolates from 98 subjects) were 8 and 128, respectively. The MIC50 and MIC90 of tobramycin for all PA isolates (151 isolates from 99 subjects) were 2 and 32, respectively.

All subjects (100.0%) in both treatment groups experienced at least 1 acute respiratory exacerbation requiring IV antibiotic treatment in the 12 months prior to screening. The proportion

of subjects experiencing 1, 2 or > 3 exacerbations, respectively, in the AZLI group were 22 (52.4%), 9 (21.4%), and 11 (26.2%) of 42 subjects and in the placebo group were 27 (58.7%), 6 (13.0%), and 13 (28.3%) of 46 subjects.

Table 2: GS-US-205-0170: Baseline Disease Characteristics

	AZLI 75 mg TID (N=42)	Placebo (N=46)	Total (N=88)	P-Value[a]
Height (cm)				
N	42	46	88	0.34
Mean (SD)	161.8 (12.30)	165.1 (11.77)	163.5 (12.07)	
Median	163.3	163.9	163.9	
Q1, Q3	154.9, 171.4	158.4, 171.4	155.7, 171.4	
Min, Max	125.5, 183.4	125.8, 189.3	125.5, 189.3	
Weight (kg) at Day -28				
N	42	46	88	0.56
Mean (SD)	56.9 (15.06)	58.5 (13.71)	57.8 (14.31)	
Median	56.8	57.5	57.1	
Q1, Q3	47.2, 64.8	50.2, 69.2	48.4, 66.5	
Min, Max	24.1, 109.8	22.0, 89.1	22.0, 109.8	
Weight (kg) at Day 1				
N	42	46	88	0.58
Mean (SD)	56.9 (14.79)	58.4 (13.58)	57.7 (14.11)	
Median	56.6	57.1	56.6	
Q1, Q3	48.0, 65.1	50.3, 67.1	48.4, 65.9	
Min, Max	25.0, 108.6	22.5, 87.2	22.5, 108.6	
BMI (kg/m^2) at Day -28				
N	42	46	88	0.89
Mean (SD)	21.46 (4.300)	21.20 (3.303)	21.32 (3.791)	
Median	20.78	21.35	20.98	
Q1, Q3	19.01, 23.14	18.82, 23.43	18.94, 23.20	
Min, Max	14.32, 41.58	13.90, 28.79	13.90, 41.58	
BMI (kg/m^2) at Day 1				
N	42	46	88	0.92
Mean (SD)	21.46 (4.257)	21.16 (3.214)	21.30 (3.729)	
Median	20.58	21.09	20.61	
Q1, Q3	18.98, 22.97	19.17, 23.22	19.07, 23.19	
Min, Max	14.36, 41.13	13.99, 28.75	13.99, 41.13	

	AZLI 75 mg TID (N=42)	Placebo (N=46)	Total (N=88)	P-Value[a]
FEV_1 (L) at Day -28				
N	42	46	88	0.40
Mean (SD)	1.67 (0.665)	1.77 (0.574)	1.72 (0.617)	
Median	1.60	1.73	1.61	
Q1, Q3	1.13, 2.17	1.28, 2.25	1.20, 2.24	
Min, Max	0.59, 3.51	0.78, 2.90	0.59, 3.51	
FEV_1 (L) at Day 1				
N	42	46	88	0.51
Mean (SD)	1.64 (0.686)	1.73 (0.613)	1.69 (0.647)	
Median	1.52	1.66	1.59	
Q1, Q3	1.10, 2.14	1.23, 2.22	1.12, 2.19	
Min, Max	0.45, 3.45	0.76, 3.11	0.45, 3.45	
FEV_1 % Predicted at Day -28				
N	42	46	88	0.82
Mean (SD)	50.80 (17.241)	51.16 (14.221)	50.99 (15.643)	
Median	47.76	50.84	50.01	
Q1, Q3	36.93, 67.05	40.98, 61.77	37.71, 64.01	
Min, Max	25.57, 79.80	23.68, 79.78	23.68, 79.80	
Disease Severity at Day -28				
FEV_1 Percent Predicted > 50%	20 (47.6%)	24 (52.2%)	44 (50.0%)	0.83
FEV_1 Percent Predicted ≤ 50%	22 (52.4%)	22 (47.8%)	44 (50.0%)	
FEV_1 % Predicted at Day 1				
N	42	46	88	0.96
Mean (SD)	49.87 (17.704)	50.09 (15.257)	49.99 (16.374)	
Median	49.99	49.02	49.14	
Q1, Q3	34.09, 66.61	39.21, 59.19	36.22, 61.32	
Min, Max	21.42, 81.08	21.94, 81.64	21.42, 81.64	
Disease Severity at Day 1				
FEV_1 Percent Predicted > 50%	21 (50.0%)	20 (43.5%)	41 (46.6%)	0.67
FEV_1 Percent Predicted ≤ 50%	21 (50.0%)	26 (56.5%)	47 (53.4%)	

	AZLI 75 mg TID (N=42)	Placebo (N=46)	Total (N=88)	P-Value[a]
FVC (L) at Day -28				
N	42	46	88	0.80
Mean (SD)	2.87 (0.929)	2.92 (0.879)	2.90 (0.898)	
Median	3.06	2.79	2.96	
Q1, Q3	2.26, 3.45	2.31, 3.58	2.29, 3.48	
Min, Max	1.25, 5.50	0.93, 5.72	0.93, 5.72	
FVC (L) at Day 1				
N	42	46	88	0.85
Mean (SD)	2.85 (0.991)	2.83 (0.886)	2.84 (0.933)	
Median	2.90	2.71	2.79	
Q1, Q3	2.14, 3.47	2.22, 3.49	2.20, 3.47	
Min, Max	0.93, 5.67	0.90, 5.11	0.90, 5.67	
FEF_{25-75} (L/sec) at Day -28				
N	42	46	88	0.47
Mean (SD)	0.88 (0.560)	0.93 (0.502)	0.91 (0.528)	
Median	0.69	0.85	0.78	
Q1, Q3	0.43, 1.39	0.48, 1.29	0.48, 1.32	
Min, Max	0.21, 2.29	0.29, 2.59	0.21, 2.59	
FEF_{25-75} (L/sec) at Day 1				
N	42	45	87	0.30
Mean (SD)	0.83 (0.519)	0.98 (0.655)	0.91 (0.595)	
Median	0.67	0.81	0.75	
Q1, Q3	0.42, 1.30	0.49, 1.27	0.45, 1.29	
Min, Max	0.19, 2.04	0.26, 3.05	0.19, 3.05	
CFQ-R RSS Score at Day -28				
N	41	45	86	0.27
Mean (SD)	65.65 (16.336)	60.56 (17.959)	62.98 (17.295)	
Median	66.67	61.11	66.67	
Q1, Q3	55.56, 77.78	50.00, 77.78	50.00, 77.78	
Min, Max	22.22, 100.00	16.67, 88.89	16.67, 100.00	

	AZLI 75 mg TID (N=42)	Placebo (N=46)	Total (N=88)	P-Value[a]
CFQ-R RSS Score at Day 1				
N	41	46	87	0.16
Mean (SD)	60.23 (18.336)	64.19 (15.206)	62.32 (16.772)	
Median	58.33	66.67	61.11	
Q1, Q3	50.00, 72.22	55.56, 72.22	50.00, 72.22	
Min, Max	22.22, 94.44	16.67, 94.44	16.67, 94.44	
Sweat Chloride Test (mEq/L)				
N	26	33	59	0.94
Mean (SD)	103.8 (20.78)	102.2 (17.97)	102.9 (19.11)	
Median	104.0	104.0	104.0	
Q1, Q3	91.0, 116.0	95.0, 114.0	94.0, 115.0	
Min, Max	44.0, 143.0	46.0, 126.0	44.0, 143.0	
CFTR Genotype				
Total subjects assessed	41	42	83	0.007
Homozygous ΔF508	21 (51.2%)	16 (38.1%)	37 (44.6%)	
Heterozygous ΔF508	17 (41.5%)	19 (45.2%)	36 (43.4%)	
Unidentified	0	7 (16.7%)	7 (8.4%)	
Other	3 (7.3%)	0	3 (3.6%)	
Azithromycin Use during Comparative Phase[b]				
No	8 (19.0%)	10 (21.7%)	18 (20.5%)	0.80
Yes	34 (81.0%)	36 (78.3%)	70 (79.5%)	
Subjects Who Used Any Inhaled Antibiotic for Maintenance Therapy in the 12 Months Prior to Enrollment	33 (78.6%)	36 (78.3%)	69 (78.4%)	–

BMI = body mass index; CFQ-R = Cystic Fibrosis Questionnaire–Revised; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in the first second; FEF_{25-75} = forced expiratory flow from 25% to 75% of the forced vital capacity; FVC = forced vital capacity; RSS = Respiratory Symptom Scale

a P-values are from a two-sided Fisher exact test for categorical variables and a Wilcoxon rank-sum test for continuous variables.

b Azithromycin use categories were based on subjects who used/did not use azithromycin at baseline and/or concomitantly during the comparative study

Source: Section 15.1, Table 9 and Table 16; Appendix 16.2, Listings 9, 10, and 13

Mean (SD) FEV1 percent predicted was 49.87 (17.704) in the AZLI group versus 50.09 (15.257) in the placebo group. Half of the subjects in the AZLI group had a baseline disease severity of FEV1 ≤ 50% predicted (21 of 42 subjects, 50.0%) versus 26 of 46 subjects (56.5%) in the placebo group. Mean (SD) baseline CFQ-R RSS score was 60.23 (18.336) for the AZLI group and 64.19 (15.206) for the placebo group. A similar proportion of subjects in the AZLI group (78.6%, 33 of 42 subjects) and the placebo group (78.3%, 36 of 46 subjects) had used an inhaled antibiotic in the 12 months prior to enrollment for maintenance therapy.

For 38 subjects (95.0%) in the AZLI group and 42 subjects (95.5%) in the placebo group, PA was present at Day 1. Mean (SD) log10 PA CFU/g of sputum for subjects with PA present at Day 1 was 5.97 (1.452) for the AZLI group and 6.25 (1.454) for the placebo group. The MIC50 and MIC90 of aztreonam for all PA isolates at Day 1 (60 isolates from 38 subjects) in the AZLI group were 4 and 64, respectively, and for the placebo group (68 isolates from 41 subjects) were 4 and 256, respectively. The MIC50 and MIC90 of tobramycin for all PA isolates for the AZLI group were 2 and 64, respectively, and for the placebo group were 2 and 32, respectively.

For the ITT Analysis Set and the Comparative Safety Analysis Set, Day 1 baseline disease characteristics were similar between treatment groups, with the exception of the distribution of CFTR genotype (p = 0.008 and p = 0.007, for each analysis set, respectively). Of the 41 subjects in the Comparative Safety Analysis Set for whom CFTR genotype was determined at baseline (Day 1) in the AZLI group, most were homozygous ΔF508 (21 subjects, 51.2%) or heterozygous ΔF508 (17 subjects, 41.5%), while CFTR genotype was categorized as other for 3 subjects (7.3%). Of the 42 subjects for whom CFTR genotype was determined at baseline in the placebo group, most were heterozygous ΔF508 (19 subjects, 45.2%) or homozygous ΔF508 (16 subjects, 38.1%), while CFTR genotype was unidentified for 7 subjects (16.7%).

Efficacy results

Primary analyses

The primary efficacy endpoint was the rate of PDEs from Day 1 through Week 24, characterized by the investigator 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 IV or inhaled antibiotics and verified by a blinded independent adjudication committee. Based on the ITT Analysis Set, the rate of PDEs was numerically lower in the AZLI group (1.309 PDEs per subject year) than in the placebo group (1.762 PDEs per subject year). This represents a 25.7% reduction in exacerbation rate for the AZLI group, although the difference between groups was not statistically significant (p = 0.25, risk ratio 0.743, 95% CI [0.446, 1.238] by negative binomial regression model).

Sensitivity analyses of the primary endpoint, including nonparametric analyses, Poisson regression analyses, and multiple event analyses were consistent with the primary analysis. Based on supplemental analyses, time to multiple PDEs did not differ significantly between treatment groups, although numerically the risk of exacerbation was reduced by 31.9% for the AZLI group when compared with the placebo group (hazard ratio=0.681 with a confidence interval [CI] from 0.359 to 1.291; p = 0.24).

When based upon the PP Analysis Set, the rate of PDEs was numerically lower in the AZLI group (1.272 per subject year, n = 35) than in the placebo group (1.799 per subject year, n = 39), representing a 29.3% reduction in exacerbation rate for the AZLI group, although the difference between groups was not statistically significant (p = 0.22, risk ratio 0.707, 95% CI [0.406, 1.230]).

CHMP comment

Due to the low enrolment, the study is considered underpowered and only limited conclusions can be drawn from the observed results.

The expected 6-month exacerbation rate for TIS/Placebo was 1.15. The expected 6 months exacerbation rate was 0.70 for the TIS/AZLI (approximately a 40% reduction in exacerbation rate. These rates were based upon the GS-US-205-0110 study for subjects receiving AZLI 75 mg TID and TIS 300 mg BID. The exacerbation rates observed in the present study were some what lower than expected in the placebo group (expected, 2.3 per subject per year; observed 1.8 per subject per year). The risk reduction in the AZLI group was also lower than expected (25% compared to 40% expected), however confidence intervals are wide and the trend is in the expected direction.

Based on supplemental analyses, time to multiple PDEs did not differ significantly between treatment groups, although numerically the risk of exacerbation was reduced by 25.7% for the AZLI group, the difference between groups was not statistically significant (p = 0.25, risk ratio 0.743, 95% CI [0.446, 1.238]
The observed trend is in line with the observations reported in in the initial report.

Secondary analyses

Change from Baseline in FEV1 % Predicted

Across all AZLI/placebo treatment courses, on average, actual FEV1 % predicted increased slightly from baseline in both groups. The magnitude of the adjusted mean (standard error [SE]) changes was larger in the AZLI group (1.37 [0.674]) than in the placebo group (0.04 [0.658]), although the 1.33 difference between treatment groups was not statistically significant. FEV1 % predicted generally returned towards baseline during each TIS cycle in the AZLI group.

Use of Non-study IV or Inhaled Antibiotics for PDEs

A numerically larger proportion of subjects in the placebo group (26 of 47 subjects, 55.3%) than in

the AZLI group (21 of 43 subjects, 48.8%) used non-study IV/inhaled antibiotics for PDEs from Day 1 to Week 24; the difference between treatment groups was not statistically significant.

Time to First PDE

Median (95% CI) time to first PDE was longer in the AZLI group (175.0 days [76.0, not estimable [NE]) than in the placebo group (140.0 days [90.0, NE]) (hazard ratio [95% CI]: 0.89 [0.50, 1.59]; p = 0.71), but there were no statistical differences between treatment groups.

Hospitalizations for a Respiratory Event

The rate of hospitalizations for a respiratory event was numerically higher in the placebo group (1.624 per subject year) than in the AZLI group (1.043 per subject year), representing a 35.8% reduction in the respiratory hospitalization rate for the AZLI group; however, the difference between treatment groups was not statistically significant (risk ratio [95% CI] 0.642 [0.355, 1.164], p = 0.14).

Change from Baseline in the CFQ-R RSS Score

An increase (indicating improvement) in the adjusted mean (SE) from baseline (Day 1) in CFQ-R RSS score was observed across all AZLI/placebo courses (Weeks 4, 12, and 20) in the AZLI group (1.00 [1.736]), while a decrease (indicating worsening) was observed in the placebo group (-2.06 [1.629]). The difference between treatment groups was not statistically significant. The following table summarize the results of the primary, supplementary, and secondary efficacy analyses for the ITT Analysis Set.

	AZLI 75 mg TID vs Placebo			
	AZLI 75 mg TID (N=43)	Placebo (N=47)	P-value	Risk or Hazard Ratio (95% CI)
Primary Endpoint				
Primary Endpoint: Rate of PDE per Subject Year as Determined by the Investigator and Adjudication Committee (Negative Binomial Regression Model)	1,309	1,762	0,25	0,743 (0,446, 1,238)
Supplementary Analyses				
Rate of PDE per Subject Year (Wilcoxon Rank Sum Test)				
N	43	47	0,3	–
Mean (SD)	1,4 (1,88)	1,9 (2,42)		
Median	0	2		
Q1, Q3	0,0, 2,2	0,0, 2,2		
Min, Max	0,0, 9,6	0,0, 10,7		
PDEs per Subject (Wilcoxon Rank Sum Test)				
N	43	47	0,46	–
Mean (SD)	0,6 (0,66)	0,8 (0,91)		
Median	0	1		
Q1, Q3	0,0, 1,0	0,0, 1,0		
Min, Max	0,0, 2,0	0,0, 4,0		
Number of PDEs per Subject				
0	22 (51,2%)	21 (44,7%)	–	–
1	17 (39,5%)	20 (42,6%)		
2	4 (9,3%)	3 (6,4%)		
3	0	2 (4,3%)		
4	0	1 (2,1%)		
Time to Multiple PDEs (Andersen-Gill Multiplicative			0,24	0,681

Hazard Model)				(0,359, 1,291)
Total Number of PDEs	25	36	–	–
Average Actual Change from Baseline (Day 1) in FEV1 % Predicted across all AZLI/Placebo Courses (Week 4, 12, 20)				
N	42	45	0,16	1,33 (-0,55, 3,20)
Mean (SD)	1,39 (4,702)	0,11 (3,862)		
Median	1,47	0,27		
Q1, Q3	-1,52, 2,89	-1,91, 1,64		
Min, Max	-8,53, 11,61	-9,49, 9,21		
Adj. Mean	1,37	0,04		
SE	0,674	0,658		
95% CI	0,03, 2,71	-1,26, 1,35		
Subjects Who Used Nonstudy IV or Inhaled Antibiotics for PDEs (Day 1 through Week 24)	21 (48,8%)	26 (55,3%)	0,67	–
Time to First PDE				
Median Days (95% CI)	175,0 (76,0, NE)	140,0 (90,0, NE)	0,71	–
Q1, Q3	64,0, NE	58,0, NE		
Total Number Censored	22	21		
Total Number of Events	21	26		
Hazard Ratio (95% CI)	0,89 (0,50,1,59)	–		
Rate of Hospitalization for a Respiratory Event per Subject Year (Day 1 through Week 24)	1,043	1,624	0,14	0,642 (0,355, 1,164)
Average Change from Baseline (Day 1) in CFQ-R RSS across all AZLI/Placebo Courses (Week 4, 12, 20)				
N	39	45	0,21	3,06 (-1,71, 7,82)
Mean (SD)	1,99 (12,523)	-2,89 (12,726)		
Median	3,7	-1,85		
Q1, Q3	-7,41, 11,11	-11,11, 3,70		
Min, Max	-27,78, 25,00	-29,63, 38,89		
Adj. Mean	1	-2,06		
SE	1,736	1,629		
95% CI	-2,46, 4,45	-5,30, 1,19		

Exploratory Endpoints:

Exploratory endpoints included change from baseline in pulmonary function tests, individual CFR-Q domains, EQ-5D utility index score and VAS, CFRSD-CRISS weekly average score, BMI, and weight. Additional exploratory endpoints were respiratory hospitalizations (percent of subjects with respiratory hospitalizations, number and percent of days hospitalized due to respiratory events, and time to first respiratory hospitalization); use of non-study antibiotics for PDEs; and missed school/work days.

Change from Baseline in FEV1 % Predicted (Additional Analyses)

As observed for the secondary endpoint of actual change from baseline in FEV1 % predicted across all AZLI/placebo courses, the difference between treatment groups in adjusted mean actual change from baseline (Day 1) in FEV1 % predicted was not statistically significant when averaged across all TIS courses or all visits.

When data were censored after any IV or inhaled nonstudy antibiotic use for PDEs, adjusted mean (SE) actual change from baseline averaged across all AZLI/placebo courses was 1.19 (0.834) in the AZLI group and -1.34 (0.784) in the placebo group (treatment difference [95% CI], 2.53 [0.25, 4.80]; p = 0.030). Adjusted mean actual change from baseline was also significantly different between treatment groups when averaged across all TIS courses (treatment difference [95% CI], 2.23 [0.13, 4.32]; p = 0.037), and all visits (treatment difference [95% CI], 2.38 [0.36, 4.40]; p = 0.022), with improvements (increases) seen in the AZLI group and worsening (decreases) observed in the placebo group.

When data were censored after any non-study antibiotic use (oral, inhaled, or IV) for exacerbations, a larger treatment difference was observed than in the analysis in which such data were not censored, but the difference was not statistically significant.

The same trends were observed in each of these analyses when relative change from baseline in FEV1 % predicted was analysed.

Change from Baseline in Individual CFQ-R Domains

The difference between treatment groups was not statistically significant when averaged across all AZLI/placebo courses, all TIS courses, or all visits for any individual CFQ-R domain except for the eating disturbances domain and the vitality domain. For the eating disturbances domain, reductions and slight increases in mean adjusted scores were observed for the placebo group and AZLI group, respectively (p = 0.032, p = 0.039, and p = 0.024, for all AZLI/placebo courses, all TIS courses, and all visits, respectively). For the vitality domain averaged across all AZLI/placebo courses, reductions and slight increases in mean adjusted scores were observed for the placebo group and AZLI group, respectively (p = 0.007); across all visits there were decreases in both groups, with a larger adjusted mean decrease in the placebo group (p = 0.032).

Change from Baseline in EQ-5D Utility Index Score and Visual Analog Scale

There was very little change from baseline (Day 1) in EQ-5D utility index or VAS in both treatment groups, and the differences between treatment groups in EQ-5D utility index score and EQ-5D VAS were not statistically significant when averaged across all AZLI/placebo courses, all TIS courses, or all visits.

Change from Baseline in CFRSD-CRISS Scores

Mean (SD) baseline CFRSD-CRISS weekly average score was 33.9 (12.78) in the AZLI group and 28.4 (12.19) in the placebo group. The mean (SD) CFRSD-CRISS weekly average score for AZLI tended to be nominally reduced from baseline with the exception of Week 20, whereas the weekly average score for placebo varied across the study period with increase from baseline observed for most of the weeks. Mean (SD) change from baseline in CFRSD-CRISS weekly average score for those subjects without exacerbations (22 subjects, AZLI group and 21 subjects, placebo group) was similar to that observed in all ITT subjects. For subjects with an exacerbation, mean (SD) change from baseline in the average score within 7 and 14 days prior to the first exacerbation was similar in the AZLI and placebo groups.

Percent of Subjects with Respiratory Hospitalizations and Number of Days Hospitalized due to Respiratory Events

Of the 60 hospitalizations reported during the comparative treatment phase of the study, 53 were respiratory hospitalizations as determined by the adjudication committee (20, AZLI and 33, placebo). A larger proportion of subjects in the placebo group (21 of 47, 44.7%) than in the AZLI group (17 of 43, 39.5%) were hospitalized at least once for respiratory events. For all subjects

(hospitalized or not hospitalized), the mean (SD) number of days hospitalized for respiratory events was lower in the AZLI group (5.7 [8.13]) than in the placebo group (8.3 [13.01]). This difference was not statistically significant.

Percent of Subjects Using Nonstudy IV or Inhaled Antibiotics in the Comparative Treatment Phase
As noted in the discussion of the secondary endpoints, a smaller proportion of subjects in the AZLI group (21 of 43 subjects, 48.8%) than in the placebo group (26 of 47 subjects, 55.3%) used nonstudy IV or inhaled antibiotics specifically for PDEs during the comparative treatment period; the difference between treatment groups was not statistically significant.

Change from Baseline in BMI/Weight
For adjusted mean change from baseline in BMI and body weight, the difference between treatment groups was not statistically significant when averaged across all AZLI/placebo courses, across all TIS courses, or across all visits.

Missed School/Work Days
The proportions of subjects who missed school or work at least once were not statistically significantly different in the AZLI group (18 of 43 subjects, 54.5%) versus the placebo group (15 of 47 subjects, 42.9%). The mean (SD) number of days that subjects missed school or work was similar between the AZLI group (7.9 [13.05]) and the placebo group (5.4 [11.74]).

CHMP comment:
Rates of respiratory hospitalizations were reduced by 35.8% in subjects treated with an AZLI/TIS CAT regimen compared to those with a placebo/TIS regimen, although no statistical differences were detected. Improvements in lung function were observed while subjects were treated with AZLI, with the highest improvement observed during the first 28-day treatment cycle. Lung function improvement was not maintained when these subjects alternated on TIS.

Overall the trend observed in analysis the primary endpoint was also reported for the secondary endpoints. Overall, the study does not allow to draw robust conclusions for efficacy due to the limited power, and non-significant findings for the primary endpoint which is a result of the low number of patients enrolled.

Efficacy in Subgroups:
The primary efficacy endpoint and associated sensitivity analyses were summarized for the ITT Analysis Set in several subgroups, including sex (male versus female); disease severity (FEV1 > 50% predicted, FEV1 ≤ 50% predicted); age (< 18 years, ≥ 18 years; 6 to 12 years, 13 to 17 years); previous exacerbations (1, 2, and ≥ 3); and azithromycin use (yes, no). No statistically significant differences between treatment groups were observed for the primary efficacy endpoint and associated sensitivity analyses in any of the subgroups analysed.

Selected secondary efficacy endpoints of actual and relative change in FEV1 % predicted and actual change in FEV1 (L), as well as change from baseline in CFQ-R RSS score for child/teen/adult were analysed by azithromycin use (yes, no). It should be noted that the subject numbers were small for the azithromycin-no groups (AZLI n = 8, placebo n = 10). Differences between treatment groups were generally not statistically significant for these secondary efficacy endpoints in the subgroups analyzed. For average percent relative change in FEV1 % predicted across all AZLI/placebo courses there was a statistically significant difference between treatment groups for those without azithromycin use (adjusted mean [SE] for the AZLI group, 6.12 [2.955] and for the placebo group, -3.43 [2.638]) (p = 0.031; difference [95% CI], 9.55 [1.03, 18.07])

CHMP comment:

No statistically significant differences between treatment groups were observed for the primary efficacy endpoint and associated sensitivity analyses in any of the subgroups analysed, including sex (male versus female); disease severity (FEV1 > 50% predicted, FEV1 ≤ 50% predicted); age (< 18 years, ≥ 18 years; 6 to 12 years, 13 to 17 years); previous exacerbations (1, 2, and ≥ 3); and azithromycin use (yes, no)..

Microbiology Results:

Sputum PA Density:

Insignificant differences between treatment groups were observed in changes in sputum PA density over the comparative treatment phase. In both the AZLI and placebo groups, increases and decreases from baseline in sputum density never exceeded 0.5 log10 CFU/g, with the largest difference between groups observed at Week 16.

Presence or Absence of Respiratory Pathogens:

Greater than 95.0% of all subjects were culture positive for PA at baseline (Day 1) in both treatment groups.

The percentages of subjects with Achromobacter spp, S. maltophilia, MSSA, or Aspergillus spp present at 1 or more visits from Week 4 through 24 were similar between treatment groups. The percentage of subjects with MRSA present at 1 or more visits was higher in the placebo group (40.0%, 18 of 45 subjects) than in the AZLI group (26.2%, 11 of 42 subjects). Burkholderia spp were isolated only in 1 subject (AZLI group) from Week 16 through Week 24.

MIC50 of Aztreonam and Tobramycin for all PA Isolates:

The aztreonam MIC50 for all PA isolates (4 µg/mL) was identical at baseline in both treatment groups and remained unchanged (≤ 2-fold changes) in both groups throughout the study. The tobramycin MIC50 for all PA isolates (2 µg/mL) was identical at baseline in both treatment groups and remained unchanged (≤ 2-fold changes) in both groups throughout the study.

MIC50 of Other Antibiotics for all PA Isolates:

At baseline (Day 1), the MIC50 of other antibiotics (amikacin, cefepime, ceftazidime, ciprofloxacin, meropenem, piperacillin, piperacillin/tazobactam, and ticarcillin/clavulanate) for all PA isolates were identical or within a 2-fold difference between treatments groups.

The MIC50 of amikacin, cefepime, ceftazidime, ciprofloxacin, meropenem, piperacillin, piperacillin/tazobactam, and ticarcillin/clavulanate for all PA isolates remained unchanged (≤ 2-fold increase or decrease) from baseline through Week 24 except for the piperacillin MIC50, which increased at Week 20 in the AZLI group; and the piperacillin/tazobactam MIC50, which increased in the AZLI group at Week 16.

PA Resistance by Antibiotic Class:

At baseline (Day 1) a higher percentage of subjects in the placebo group (26.2%, 11 of 42 subjects) than in the AZLI group (12.8%, 5 of 39 subjects) had PA isolates with antibiotic resistance to all 6 beta-lactams. Thereafter, the percentages were similar between treatment groups with the exception of Week 16, when the percentage was notably higher in the AZLI group (23.7%, 9 of 38 subjects) than in the placebo group (10.0%, 3 of 30 subjects).

At baseline, the percentages of subjects with multi-drug resistant PA having resistance to at least 1 of the antibiotics in 2 of the 3 drug classes were similar between treatment groups, but for subjects

with multi-drug resistant PA having resistance to all antibiotics tested in 2 of the 3 drug classes (CFF definition), baseline percentages were higher in the placebo group (38.1%, 16 of 42 subjects) than in the AZLI group (20.5%, 8 of 39 subjects). Thereafter, the percentages were similar between treatment groups for both definitions of multi-drug resistance with the exception of Week 16 for the CFF definition, when the percentage was notably higher in the AZLI group (36.8%, 14 of 38 subjects) than in the placebo group (23.3%, 7 of 30 subjects).

CHMP comment

No significant differences between treatment groups were observed in changes in sputum PA density over the comparative treatment phase. No concerning changes in the susceptibility of all PA isolates to aztreonam, tobramycin, and to other antibiotics were observed, and no concerning trends were observed in the treatment-emergent isolation of other bacterial respiratory pathogens (Achromobacter spp, Burkholderia spp, S. maltophilia, MRSA, MSSA,and Aspergillus spp).

Safety results

Exposure:

TIS Run-In Phase

The mean (SD) duration of exposure to TIS in the run-in phase was 27.7 (3.22) days (TIS Run-in Safety Analysis Set [N = 107]). The mean (SD) total dose of TIS taken during the run-in phase of the study was 15,322.4 (2474.45) mg per subject.

Comparative Treatment Phase

The mean (SD) duration of exposure to AZLI or placebo across 3 cycles in the comparative-treatment phase was similar (79.2 [19.86] days for the AZLI group and 79.9 [17.10] days for the placebo group). The mean (SD) total dose taken during the comparative-treatment phase was 16,251.8 (4762.34) mg AZLI per subject in the AZLI group and 15,849.5 (4341.23) mg placebo per subject in the placebo group.

The mean (SD) duration of exposure to TIS across 3 treatment cycles in the comparative-treatment phase was 83.2 (17.11) days for the AZLI group and 74.4 (23.22) days for the placebo group. The mean (SD) total dose taken during the comparative-treatment phase was 44,535.0 (8178.38) mg TIS per subject in the AZLI group and 39,613.3 (12,652.16) mg TIS per subject in the placebo group.

Adverse Events:

TIS Run-In-Emergent Adverse Events

TIS run-in-emergent AEs were reported for 44.9% of subjects (48 of 107). The most commonly reported TIS run-in□emergent AEs were cough (19.6%, 21 subjects), sputum increased (11.2%, 12 subjects), and dyspnea (8.4%, 9 subjects). Grade 3 or 4 AEs were reported for 2 subjects (1.9%). Treatment-related TIS run-in-emergent AEs were reported for 3 subjects (2.8%); none of these AEs was Grade 3 or 4.

Comparative-Phase Adverse Events

Comparative-phase AEs were reported for a similar percentage of subjects in each treatment group (95.2%, 40 of 42 subjects in the AZLI group; 97.8%, 45 of 46 subjects in the placebo group).

In both treatment groups, the most commonly reported comparative-phase AEs were cough (AZLI, 76.2%, 32 subjects; placebo, 71.7%, 33 subjects), sputum increased (AZLI, 47.6%, 20 subjects; placebo, 67.4%, 31 subjects), and dyspnea (AZLI, 31.0%, 13 subjects; placebo, 52.2%, 24 subjects). Dyspnea and sputum increased were reported more commonly (> 10% difference) in the

placebo group compared with the AZLI group. Nasal congestion occurred more commonly (> 10% difference) in the AZLI group (26.2%, 11 subjects) compared with the placebo group (8.7%, 4 subjects). Infective pulmonary exacerbation of CF (within the infections and infestations SOC) was reported more commonly in the AZLI group (23.8%, 10 subjects) compared with the placebo group (10.9%, 5 subjects).

A lower percentage of subjects (> 10% difference) in the AZLI group compared with the placebo group experienced AEs of fatigue (AZLI, 26.2%, 11 subjects; placebo, 37.0%, 17 subjects) and exercise tolerance decreased (AZLI, 7.1%, 3 subjects; placebo, 26.1%, 12 subjects).

Decreased appetite was reported for a lower percentage of subjects (> 20% difference) in the AZLI group (11.9%, 5 subjects) compared with the placebo group (34.8%, 16 subjects). Infective exacerbation of CF and many of the individual respiratory and other signs/symptoms listed here are indicative of pulmonary exacerbations; differences may represent reporting preferences of the investigators. All AEs associated with pulmonary exacerbations were evaluated by the blinded, independent adjudication committee as part of the primary endpoint determination.

Table 5. GS-US-205-0170: Comparative-Phase Treatment-Emergent Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group (Comparative Safety Analysis Set)

System Organ Class Preferred Term	AZLI 75 mg TID (N=42)	Placebo (N=46)	Total (N=88)
Subjects with any comparative phase AEs	40 (95,2%)	45 (97,8%)	85 (96,6%)
Gastrointestinal disorders	17 (40,5%)	13 (28,3%)	30 (34,1%)
Nausea	6 (14,3%)	10 (21,7%)	16 (18,2%)
Diarrhoea	6 (14,3%)	5 (10,9%)	11 (12,5%)
Vomiting	5 (11,9%)	9 (19,6%)	14 (15,9%)
Abdominal pain	4 (9,5%)	1 (2,2%)	5 (5,7%)
Constipation	4 (9,5%)	0	4 (4,5%)
General disorders and administration site conditions	23 (54,8%)	35 (76,1%)	58 (65,9%)
Fatigue	11 (26,2%)	17 (37,0%)	28 (31,8%)
Pyrexia	8 (19,0%)	13 (28,3%)	21 (23,9%)
Chest discomfort	8 (19,0%)	13 (28,3%)	21 (23,9%)
Chest pain	4 (9,5%)	7 (15,2%)	11 (12,5%)
Chills	3 (7,1%)	5 (10,9%)	8 (9,1%)
Exercise tolerance decreased	3 (7,1%)	12 (26,1%)	15 (17,0%)
Infections and infestations	18 (42,9%)	18 (39,1%)	36 (40,9%)
Infective pulmonary exacerbation of cystic fibrosis	10 (23,8%)	5 (10,9%)	15 (17,0%)
Bronchopneumonia	1 (2,4%)	3 (6,5%)	4 (4,5%)
Investigations	20 (47,6%)	15 (32,6%)	35 (39,8%)
Pulmonary function test decreased	11 (26,2%)	10 (21,7%)	21 (23,9%)
Weight decreased	4 (9,5%)	5 (10,9%)	9 (10,2%)
FEV1 decreased	4 (9,5%)	2 (4,3%)	6 (6,8%)
Metabolism and nutrition disorders	8 (19,0%)	16 (34,8%)	24 (27,3%)
Decreased appetite	5 (11,9%)	16 (34,8%)	21 (23,9%)
Musculoskeletal and connective tissue disorders	11 (26,2%)	8 (17,4%)	19 (21,6%)
Back pain	3 (7,1%)	4 (8,7%)	7 (8,0%)
Nervous system disorders	11 (26,2%)	12 (26,1%)	23 (26,1%)

Headache	7 (16,7%)	8 (17,4%)	15 (17,0%)
Sinus headache	3 (7,1%)	2 (4,3%)	5 (5,7%)
Psychiatric disorders	5 (11,9%)	4 (8,7%)	9 (10,2%)
Anxiety	3 (7,1%)	3 (6,5%)	6 (6,8%)
Respiratory, thoracic and mediastinal disorders	37 (88,1%)	43 (93,5%)	80 (90,9%)
Cough	32 (76,2%)	33 (71,7%)	65 (73,9%)
Sputum increased	20 (47,6%)	31 (67,4%)	51 (58,0%)
Dyspnoea	13 (31,0%)	24 (52,2%)	37 (42,0%)
Haemoptysis	11 (26,2%)	11 (23,9%)	22 (25,0%)
Respiratory tract congestion	11 (26,2%)	11 (23,9%)	22 (25,0%)
Nasal congestion	11 (26,2%)	4 (8,7%)	15 (17,0%)
Lung disorder	9 (21,4%)	13 (28,3%)	22 (25,0%)
Wheezing	9 (21,4%)	9 (19,6%)	18 (20,5%)
Oropharyngeal pain	6 (14,3%)	5 (10,9%)	11 (12,5%)
Rhinorrhoea	5 (11,9%)	8 (17,4%)	13 (14,8%)
Sputum discoloured	5 (11,9%)	3 (6,5%)	8 (9,1%)
Dyspnoea exertional	5 (11,9%)	2 (4,3%)	7 (8,0%)
Dysphonia	4 (9,5%)	2 (4,3%)	6 (6,8%)
Sinus congestion	3 (7,1%)	7 (15,2%)	10 (11,4%)
Rales	3 (7,1%)	1 (2,2%)	4 (4,5%)
Upper-airway cough syndrome	2 (4,8%)	4 (8,7%)	6 (6,8%)
Increased viscosity of bronchial secretion	1 (2,4%)	4 (8,7%)	5 (5,7%)
Paranasal sinus hypersecretion	1 (2,4%)	3 (6,5%)	4 (4,5%)
Productive cough	0	3 (6,5%)	3 (3,4%)
Pleuritic pain	0	3 (6,5%)	3 (3,4%)
Skin and subcutaneous tissue disorders	12 (28,6%)	8 (17,4%)	20 (22,7%)
Rash	4 (9,5%)	1 (2,2%)	5 (5,7%)
Pruritus	3 (7,1%)	1 (2,2%)	4 (4,5%)
Night sweats	3 (7,1%)	0	3 (3,4%)

Adverse events were mapped according to MedDRA 17.1.
Treatment-emergent for the comparative phase was defined as starting on or after the AZLI or placebo first dose date through 30 days after last dose.
Subjects were counted only once for each PT. Subjects with multiple PTs within a SOC are counted only once for the SOC.

Adverse Events by Age and Gender:

No remarkable differences were noted in analyses of comparative-phase AEs by age (18 years, ≥ 18 years, ≥ 6 years to ≤ 12 years, and > 12 years to < 18 years) and gender (male, female).

Adverse Events by Severity:

Comparative-phase Grade 3 or 4 AEs were reported for a similar percentage of subjects in each treatment group (AZLI, 31.0%, 13 subjects; placebo, 30.4%, 14 subjects). The most commonly reported comparative-phase Grade 3 or 4 AEs were as follows: lung disorder (14.3%, 6 subjects), infective pulmonary exacerbation of CF (9.5%, 4 subjects), cough (7.1%, 3 subjects), and dyspnea and sputum increased (4.8%, 2 subjects, each) in the AZLI group; and lung disorder (10.9%, 5 subjects), infective pulmonary exacerbation of CF (8.7%, 4 subjects), and cough and dyspnea (4.3%, 2 subjects, each) in the placebo group.

Adverse Events by Relationship to Study Treatment:

Treatment-related comparative-phase AEs were reported for a similar percentage of subjects in each treatment group (AZLI, 7.1%, 3 subjects; placebo, 6.5%, 3 subjects). The most commonly reported comparative-phase AEs considered related to study treatment (AZLI/placebo or TIS) were cough (AZLI, 4.8%, 2 subjects; placebo, 4.3%, 2 subjects) and chest discomfort (AZLI, 0 subjects; placebo, 4.3%, 2 subjects). None of the comparative-phase Grade 3 or 4 AEs was assessed by the investigator to be related to study treatment.

Adverse Events of Interest:

Decreased pulmonary function (including the preferred terms pulmonary function test decreased and FEV1 decreased) was experienced by 33.3% of subjects in the AZLI group and 26.1% of subjects in the placebo group (Comparative Safety Analysis Set). Shortness of breath (including the preferred terms: exercise tolerance decreased, dyspnea, and dyspnea exertional) was experienced by 38.1% of subjects in the AZLI group and 60.9% of subjects in the placebo group (Comparative Safety Analysis Set).

Death:

One subject (AZLI group) died on study Day 199 due to end-stage CF lung disease with self-induced alcohol poisoning with cardiorespiratory failure secondary to Pseudomonas sepsis from a central line infection. No subject died during the TIS run-in safety phase.

Serious Adverse Events:

TIS Run-In-Emergent Serious Adverse Events

Overall, 3.7% of subjects (4 of 107) experienced TIS run-in-emergent SAEs. Two subjects had SAEs of infective pulmonary exacerbation of CF, 1 subject had an SAE of pneumonia, and 1 subject had an SAE of lung disorder. None of the TIS run-in-emergent SAEs was considered related to TIS or study procedure.

Comparative-Phase Serious Adverse Events

Comparative-phase SAEs were reported for a similar percentage of subjects in each treatment group (50.0%, 21 subjects in the AZLI group and 52.2%, 24 subjects in the placebo group). Serious adverse events of lung disorder occurred less commonly in the AZLI group (21.4%, 9 subjects) compared with the placebo group (28.3%, 13 subjects). Serious adverse events of infective pulmonary exacerbation of CF occurred more commonly in the AZLI group (21.4%, 9 subjects) compared with the placebo group (10.9%, 5 subjects). The only other SAE reported for > 1 subject in either treatment group was bronchopneumonia (AZLI, 2.4%, 1 subject; placebo, 6.5%, 3 subjects). None of the comparative-phase SAEs was considered treatment related, and none led to permanent discontinuation of study drug.

Discontinuations Due to Adverse Events:

TIS Run-In Phase

TIS run-in-emergent AEs leading to TIS discontinuation were reported for 5.6% of subjects (6 of 107). The most commonly reported TIS run-in-emergent AEs leading to TIS discontinuation were cough (5 subjects, 4.7%), dyspnea (3 subjects, 2.8%), and sputum increased and chest discomfort (2 subjects, 1.9%, each). One subject experienced AEs of pulmonary pain, chest discomfort, cough, and wheezing, which were considered related to TIS, that led to TIS withdrawal and discontinuation from the study. None of the other TIS run-in-emergent AEs leading to TIS discontinuation was considered by the investigator to be related to TIS.

Comparative Treatment Phase

One subject (2.4% for AZLI and 2.2% for placebo) in each treatment group experienced comparative-phase AEs leading to permanent discontinuation of study treatment. In the AZLI group, 1 subject discontinued from the comparative treatment phase due to Grade 2 AEs of pulmonary mycosis and cough. The AE of cough began during the TIS run-in phase. In the placebo group, 1 subject discontinued due to a Grade 2 AE of FEV1 decreased. All of the comparative-phase AEs leading to discontinuation of study treatment were considered by the investigator to be nonserious and not related to study drug or study procedure, rather due to pulmonary exacerbation.

Clinical Laboratory Evaluations:

Most laboratory abnormalities were Grade 1 or 2. Grade 1 laboratory abnormalities occurred in 32.5% of subjects (13 of 40) in the AZLI group and 43.9% of subjects (18 of 41) in the placebo group. Grade 2 laboratory abnormalities occurred in 10.0% of subjects (4 of 40) in the AZLI group and 12.2% of subjects (5 of 41) in the placebo group. Grade 3 laboratory abnormalities occurred in 10.0% of subjects (4 of 40) in the AZLI group and 2.4% of subjects (1 of 41) in the placebo group. The only Grade 3 laboratory abnormality to occur in > 1 subject overall was elevated glucose (AZLI, 2 subjects; placebo, 1 subject). No subject in the Comparative Analysis Set had a Grade 4 laboratory abnormality. No subject in the Comparative Safety Analysis Set with a postbaseline laboratory measurement (AZLI: n = 40; placebo: n = 41) had a marked laboratory abnormality.

There were no clinically relevant changes from baseline (screening) in hematology or chemistry parameters at the end of the study.

Body Weight and Vital Signs:

There were no clinically meaningful mean changes from Day -28 to baseline and from baseline to Weeks 4, 8, 12, 16, 20, and 24 in body weight, BMI, or vital signs (heart rate, systolic and diastolic blood pressure, body temperature, and respiratory rate) for either treatment group during the study.

Airway Reactivity:

TIS Run-In Phase

At 30 minutes after completing an in-clinic dose of TIS on Day -28, 1 subject experienced an acute decrease of ≥ 15% in FEV1 (Run-in Safety Analysis Set).

Comparative Treatment Phase

At 30 minutes after completing an in-clinic dose of study treatment (AZLI/placebo) on Day 1, no subject experienced an acute decrease of ≥ 15% in FEV1 (Comparative Safety Analysis Set).

Pregnancy:
One pregnancy (placebo group) was reported during the study. During the pregnancy, the subject developed diabetes mellitus in the third trimester, intrauterine growth restriction during the second and third trimesters, and CF pulmonary exacerbation in the third trimester. The subject was induced at 37 weeks gestation and delivered a preterm healthy baby. It should be noted that the subject's underlying CF lung disease placed her at an increased risk of an intrauterine growth restriction.

CHMP comment: AZLI was tolerated over 3 treatment courses, alternating with 3 courses of TIS, with an AE profile consistent with the other previously established clinical trial experience with AZLI and TIS. Predominantly respiratory AEs, consistent with the signs and symptoms of CF, were reported in the study. In both treatment groups, the most commonly reported comparative-phase AEs were cough (AZLI, 76.2%; placebo, 71.7%), sputum increased (AZLI, 47.6%; placebo, 67.4%), and dyspnea (AZLI, 31.0%; placebo, 52.2%). Overall, comparative-phase SAEs were reported for a similar percentage of subjects in each treatment group (AZLI, 50.0%; placebo, 52.2%). Overall, 1 subject (AZLI group) died due to end-stage CF lung disease and self-induced alcohol poisoning with cardiorespiratory failure secondary to Pseudomonas sepsis from a central line infection.

2.3.3. Discussion on clinical aspects

The purpose of the GS-US-205-0170study was to evaluate the safety and efficacy of a continuous alternating therapy (CAT) regimen with aztreonam for inhalation solution (AZLI) and tobramycin inhalation solution (TIS) in adult and paediatric subjects with cystic fibrosis (CF) and pulmonary Pseudomonas aeruginosa (PA) infection.

The planned sample size for this study was 250 subjects, 125 subjects per treatment group. During the enrolment period, 73 sites were activated, only 45 of which enrolled subjects. The study was ultimately closed to enrolment early because projections based on repeated feasibility surveys with the sites indicated the enrolment goals would not be reached. Enrolment was substantially hampered due to 1) competing CF trials and 2) the increasing use of CAT treatment as standard care for CF patients during the enrolment period, which resulted in patients being unwilling to enrol in a randomized, placebo-controlled trial. Of the 107 subjects enrolled, 93 subjects completed TIS run-in treatment, and a total of 90 subjects (43 in the AZLI group and 47 in the placebo group) were randomized. As a consequence, this study was underpowered.

Based upon the GS-US-205-0110 study for subjects receiving AZLI 75 mg TID and TIS 300 mg BID, a 40% reduction in exacerbation rate in the AZLI group was expected compared to the placebo group. The exacerbation rates observed in the present study were some what lower than expected in the placebo group (expected, 2.3 per subject per year; observed 1.8 per subject per year). The risk reduction in the AZLI group was also lower than expected (25% compared to 40% expected), however confidence intervals are wide and the trend is in the expected direction.

The efficacy and safety trends as observed in this study do not reveal unexpected results and can be considered in line with the results reported in the original dossier.

3. Rapporteur's overall conclusion and recommendation

The study does not allow to draw robust conclusions for efficacy, due to limitations in patient enrolment. However, there are no detrimental effects in terms of efficacy that would counteract the results of the previous studies.

No new or unexpected safety signals were observed from the study and the safety results are consistent with prior studies and the established safety profile for aztreonam.

Therefore the B/R of Cayston remains positive.

No changes in the SmPC were proposed by the MAH. Given the confirmative or indistinct results of this study no changes in the SmPC are proposed by the Rapporteur.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. Additional clarification requested

None