3 September 2012
EMA/571864/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cayston

aztreonam

Procedure No.: EMEA/H/C/000996/II/0018

Note

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

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LIST OF ABBREVIATIONS

AE	adverse event
API	active pharmaceutical ingredient
AZLI	Aztreonam Lysine
BID	twice daily
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFU	colony-forming units
CSR	clinical study report
FDA	US Food and Drug Administration
FEF_{25-75}	forced expiratory flow during the middle half of the forced vital capacity
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GRCQ	global rating of change questionnaire
HRQOL	health related quality of life
IV	Intravenous
MARPA	multiple antibiotic-resistant *PA*
MCID	minimal clinically important difference
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration for 50% of isolates
MIC_{90}	minimum inhibitory concentration for 90% of isolates
MTD	maximum tolerated dose
PA	*Pseudomonas aeruginosa*
PRO	patient reported outcome
SAE	serious adverse event
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	standard deviation
T_{max}	time to maximum concentration
TID	three times daily
TNS	Tobramycin Nebuliser Solution (TOBI)
US	United States
SaO_2	oxygen saturation

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Ltd. submitted to the European Medicines Agency on 18 August 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Cayston	aztreonam	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC in order to include paediatric patients aged 6 years and older, to include long-term, repeated use data and specifically to reflect clinical treatment outcomes.

The Package Leaflet was proposed to be updated in accordance.

The requested variation proposes amendments to the SmPC and Package Leaflet.

Rapporteur: Barbara van Zwieten-Boot

1.2. Steps taken for the assessment

Submission date:	18 August 2011
Start of procedure:	18 September 2011
Rapporteur's preliminary assessment report circulated on:	11 November 2011
Rapporteur's updated assessment report circulated on:	8 December 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	15 December 2011
MAH's responses submitted to the CHMP on:	16 February 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	2 April 2012
Rapporteur's final assessment report on the MAH's responses circulated on:	13 April 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	19 April 2012

MAH's responses submitted to the CHMP on:	21 May 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	7 June 2012
Rapporteur's final assessment report on the MAH's responses circulated on:	14 June 2012
CHMP opinion:	21 June 2012

Information on Paediatric requirements

This application has been subject to a PIP compliance verification (Compliance report EMEA-C2-000827-PIP01-09-M01).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

The PDCO issued an opinion on partial/interim compliance.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The present type II variation EMEA/H/C/000996/II/0018 pertains to

1. the extension (to include paediatric patients aged 6 years to 17 years) and rewording of the currently approved indication,
2. change of posology based on long term data and
3. to include appropriate information in sections 4.4 and 5.1 of the Summary of Product Characteristics (SmPC).

The CHMP issued a final positive Opinion for granting a conditional Marketing Authorisation to Cayston on 21 September 2009. The conditional Marketing Authorisation was renewed on 26 August 2010. On 5 September 2011 the conditional marketing authorisation was lifted in a marketing authorisation not subject to specific obligations.

The product was designated as an orphan medicinal product EU/3/04/204 on 21 June 2004.

Cayston is currently available in the following EU countries:

- from 1 April 2010 onwards: United Kingdom, Austria and Germany.
- from 10 May 2010: France
- from 20 September 2010: Denmark
- from 1 March 2011: Portugal
- from 28 March 2011: Greece
- from 01 August 2011: The Netherlands and Luxemburg

- from 01 September 2011: Spain

Furthermore Cayston is available on a named-patient or equivalent programme in several other EU countries.

Currently approved indication(s): Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa (PA)* in patients with cystic fibrosis (CF) aged 18 years and older.

The primary support for this indication is based on two single 28-day course placebo-controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited (see section 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology: The currently recommended standard dosage of Cayston is limited to adults. The recommended dose is 75 mg three times per 24 hours for 28 days. Doses should be taken at least 4 hours apart.

Multiple course, controlled efficacy data are not yet available (see section 5.1). Additional courses, beyond the initial 28-day course, should be considered only at the discretion of the physician. If additional courses are prescribed, a minimum of 28 days without Cayston is recommended.

Paediatric development

Paediatric development is ongoing in *PA* infected paediatric CF patients.

Seven phase 2/3 Gilead-sponsored clinical studies of aztreonam lysine (AZLI) which included paediatric patients aged 6 years and older have been completed (CP-AI-003, CP-AI-005, CP-AI-007, CP-AI-006, GS-US-205-0117, GS-US-205-0110 and EA-US-205-0111), and one study is ongoing (EA-US-205-0122).

The approved Cayston PIP includes an exploratory Phase 2 study (GS-US-205-XXX1 [GS-US-205-0162]), a deferral to conduct a subsequent Phase 3 study (GS US 205-XXX2) to evaluate initial *PA* infection in paediatric subjects (aged 3 months to 17 years), a Phase 3 study (GS-US-205-XXX3 [GS-US-205-0160]) to evaluate long-term safety in paediatric subjects (aged less than 13 years) with chronic *PA* infection/colonization, and completed study GS-US-205-0110, which included children with CF 6 years or older.

2.1.2. About the product

Aztreonam Lysine 75 mg Powder and solvent for Nebuliser Solution is a novel formulation of the monobactam antibiotic aztreonam, developed by Gilead for aerosol administration. Aztreonam has been approved for IV administration (Azactam) in the EU in the 1980's. The approved formulation contains approximately 780 mg arginine per gram of aztreonam. However, aerosolized arginine has been tested as a mucolytic in CF patients, and was shown to be unsafe, resulting in inflammatory adverse reactions when inhaled by CF patients. The applicant developed a lysine salt of aztreonam, Aztreonam lysine (AZLI) in order to eliminate the inflammatory component of the IV (arginine containing) formulation, making it suitable for airway administration, while preserving its antimicrobial activity against *P. aeruginosa*.

AZLI is administered with the eFlow family of electronic nebulizers (Altera) with a handset customized for the delivery of AZLI. The Altera is a nebulizer that uses a vibrating perforated membrane to generate the aerosol. Conventional nebulizers use pneumatic processes to generate the aerosol,

requiring bulky compressors or a compressed air source. The Altera creates an aerosol using a vibrating membrane that has over 4,000 holes. The membrane is driven by a piezoelectric crystal, allowing the nebulizer to be battery powered and portable.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

General comments on compliance with GMP, GLP, GCP

In the original MAA the MAH states that trials were performed with the ethical principles that are consistent with Good Clinical Practice (GCP) and according to the International Conference on Harmonisation (ICH) guidelines.

Significant problems have been detected in one of the approved manufacturing sites of the finished product, Ben Venue Laboratories Inc. at 650 Cliffside Drive in San Dimas, California. Gilead Sciences International Ltd. notified EMA about the intent to delete Ben Venue Laboratories Inc as manufacturer site (grouped type IA variation). Following review of the notification, a favourable opinion on the deletion of aforementioned manufacturer was provided on 11 May 2012.

2.1.4. Type of application and other comments on the submitted dossier

- Legal basis

C.I.6 - Change(s) to therapeutic indication(s) - a) Addition of a new therapeutic indication or modification of an approved one - Procedure type II

2.2. Quality aspects

No new data were submitted.

2.3. Non-clinical aspects

No new data were submitted.

2.4. Clinical aspects

No new efficacy data has been put forward by the Marketing Authorisation holder (MAH). Subgroup analyses of already available data in paediatric patients have been performed and evaluated separately by the MAH.

During the initial MAA, CP-AI-005, CP-AI-007 and then ongoing CP-AI-006 were assessed. In the Rapporteur's first (annual) renewal assessment report dated 31 March 2010 (EMEA/H/C/000996/R/0006), the clinical efficacy with respect to Study CP-AI-006, Study GS-US-205-0117 (AIR-CF4) and the, at that moment, ongoing Study GS-US-205-0110 were thoroughly discussed. During the last annual renewal (EMEA/H/C/000996/R/0015) Specific Obligation (SO2), Study GS-US-

205-0110 was assessed.

Furthermore, on 19 August 2011, the safety data from study EA-US-205-0111 (eCTD sequence 0076) was submitted, which is regarded as supportive.

The following sections review the efficacy data of AZLI in paediatric patients (< 18 years of age) enrolled in completed controlled efficacy studies (CP-AI-003, CP-AI-005, CP-AI-007, GS-US-205-0117, and GS-US-205-0110). In addition, while not controlled, Study CP-AI-006 was an open-label extension study of up to 9 courses of AZLI in 274 subjects who had participated in studies CP-AI-005 and CP-AI-007; therefore, data from this study are also presented. For background information a short summary is provided for each efficacy study.

- ***Tabular overview of clinical studies***

Table 1: Overview of safety/efficacy studies

	CP-AI-003	**CP-AI-005**	**CP-AI-006**	**CP-AI-007**	**GS-US-205-0110**	**GS-US-205-0117**	**GS-US-205-0111**
Study type	Dose finding; Safety/efficacy	Safety/efficacy (double blinded, placebo controlled)	Safety (open label)	Safety/efficacy (double blinded, placebo controlled)	Safety/efficacy (Double blinded , active controlled)	Safety/efficacy (double blinded, placebo controlled)	Safety (extended open label)
Total number patients include	AZLI 75 mg BID: **37** AZLI 225 mg BID: **37** Placebo: **31**	AZLI 75 mg BID: **69** AZLI 75 mg TID: **66** Placebo BID: **38** Placebo TID: **38**	AZLI 75 mg BID: **85** AZLI 225 mg TID: **189**	AZLI 75 mg TID:**80** Placebo:**84**	AZLI 75 mg: **136** TNS 300 mg BID: **132**	ALZI 75 mg TID: **76** Placebo: **81**	AZLI 75 mg TID: **603**
	Treatment for 14 days	AZLI; 75 mg BID or TID; inhalation; 28-day run-in of TNS, 28 days of AZLI, 56 days of follow-up	AZLI: 75mg BID or TID; inhalation; Up to nine 28-day courses of AZLI, each course followed by 28 days off treatment	AZLI; 75 mg TID; inhalation; 28 days of AZLI, 14 days of follow-up			
Inclusion criteria							
Age	> 13 years	≥ 6 years	≥ 6 years	≥ 6 years	≥ 6 years	≥ 6 years	≥ 6 years
FEV1% predicted	≥ 25% ≤75%	≥ 25% ≤75%	-	≥ 25% ≤75%	≤75%	>75%	-
Primary endpoints							
	percent change in FEV_1 (Day 0 to Day 14)			FEV1 < 75% predicted	FEV1 ≤ 75% predicted	FEV1 < 75% predicted	n/a
	Change in	time to need	Adverse	Change in	Change in	Change in	n/a

	log_{10} PA from baseline at day 28	IV or inhaled anti-PA antibiotics	events	log_{10} PA from baseline at day 28	log_{10} PA from baseline at day 28	log_{10} PA from baseline at day 28	
			Airway reactivity	Change in CFQ-R at day 28		change in CFQ-R RSS	n/a

2.4.1. Pharmacokinetics

Children

Literature data indicates no significant age dependency in the pharmacokinetics following i.v. administration, besides the influence of renal function.

Study -002 included adolescent CF patients, whose sputum aztreonam concentrations were evaluated after a single 75 mg inhalation dose. In studies -003, -005 and -007, children and adolescents were included, receiving b.i.d. or t.i.d. treatment of aztreonam by inhalation. Pooled data show no difference in aztreonam plasma concentrations between adolescents and adults (Table PK 1). In children there is some indication of lower aztreonam plasma concentrations. For aztreonam measured in sputum, no clear difference was observed between the different age groups.

Table PK 1: Plasma aztreonam concentrations 1 h post-dose by age in studies -003, -005 and -007.

Dose (mg) Frequency	Day	Concentration in Subjects Aged ≥ 6 to ≤ 12 (ng/mL) Mean (SD), n	Concentration in Subjects Aged > 12 to < 18 (ng/mL) Mean (SD), n	Concentration in Subjects aged ≥ 18 (ng/mL) Mean (SD), n
75 BID	0	330 (184), 4	665 (305), 21	584 (355), 78
	7	n/a	627 (362), 8	625 (349), 26
	14	294 (247), 4	633 (325), 13	640 (298), 48
225 BID	0	n/a	1635 (864), 12	1603 (835), 25
	7	n/a	1529 (1449), 12	1468 (876), 24
75 TID	0	660 (434), 10	706 (386), 19	592 (387), 106
	14	738 (418), 15	682 (461), 19	676 (345), 101
	28	525 (402), 10	494 (338), 10	713 (395), 48

No clear differences in plasma and sputum aztreonam concentrations are observed between children, adolescents and adults; however this conclusion is hampered due to the high inter-subject variability.

The proposed SmPC indicates that the posology in children > 6 years of age is the same as for adults, and that dosage is not based on weight or adjusted for age. Taking into account the indication and the low systemic exposure after inhalation, this is considered acceptable, based upon a pharmacokinetic point of view.

2.4.2. Clinical efficacy aspects

Dose-response studies and main clinical studies

Overview

GS-US-205-0110 (long term study)

In GS-US-205-0110, 268 patients with CF and chronic *P. aeruginosa* lung infection were randomised and received Cayston (N=136) or Tobramycin Nebuliser Solution (TNS) (N=132). Fifty-nine paediatric patients aged 6 to 17 years were included in the trial. Patients were randomised in a 1:1 ratio to receive either Cayston (75 mg) administered by inhalation 3 times a day or TNS (300 mg) administered 2 times a day. Treatments were administered for three cycles of 28 days on therapy followed by 28 days off therapy. The co-primary endpoints were non-inferiority of Cayston to TNS in relative change from baseline to Day 28 in Forced expiratory volume in one second (FEV1) % predicted and superiority of Cayston to TNS in actual change from baseline in FEV1 % predicted across 3 treatment courses (the average of the actual change in FEV1 % predicted observed at the end of each treatment course).

The secondary endpoints in this study were:

- Relative change from baseline in FEV1 percent predicted at Day 28 in subjects who received inhaled tobramycin for ≥84 days in the 12 months prior to study enrollment (non-inferiority analysis)
- Actual change from baseline in FEV1 percent predicted across 3 treatment courses in subjects who received inhaled tobramycin for ≥84 days in the 12 months prior to study enrollment (superiority analysis)
- Time to need for IV antipseudomonal antibiotic for respiratory events among all subjects (superiority analysis)
- Time to first respiratory hospitalisation among all subjects (superiority analysis)

The tertiary efficacy endpoints were as follows:

- Change from baseline in FEV1 percent predicted at each study visit (exclusive of Day 28)
- Change from baseline in FEV1, FVC (forced vital capacity), and FEF25-75 (forced expiratory flow during the middle half of the forced vital capacity) at each study visit
- Change from baseline in Cystic Fibrosis Questionnaire Quality of Life – Revised (CFQ R) Respiratory Symptoms Scale (RSS) at each study visit
- Change from baseline in other domains as assessed by the CFQ-R at each study visit
- Hospitalizations Days 0 to 168
- Use of additional antipseudomonal antibiotics (other than randomized treatment) Days 0 to 168
- Change in weight/body mass index (BMI) at Week 20
- Missed school/work days, Days 0 to 168
- Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 28 and either Day 140 or Early Termination (ET)

CP-AI-007

CP-AI-007 enrolled 164 adult (predominantly) and paediatric patients randomised in a 1:1 ratio comparing inhaled Cayston 75 mg (80 patients) or placebo (84 patients) administered 3 times a day for 28 days (one course). Patients were required to have been off antipseudomonal antibiotics for at least 28 days before treatment with study drug.

Pulmonary function and respiratory symptoms significantly improved from baseline to Day 28 in patients treated with one course of Cayston.

CP-AI-005

CP-AI-005 enrolled 246 adult (predominantly) and paediatric patients**.** All patients were treated with Tobramycin Nebuliser Solution (TNS) 300 mg, 2 times a day in the four weeks immediately prior to receiving Cayston or placebo either 2 or 3 times a day for 28 days. Patients continued on their baseline medications, including macrolide antibiotics. Patients were randomised in a 2:2:1:1 ratio to be treated with Cayston 75 mg 2 or 3 times a day or volume-matched placebo 2 or 3 times a day for 28 days immediately following the 28-day lead-in course of open-label TNS.

Cayston therapy resulted in significant improvements in pulmonary function and respiratory symptoms at Day 28 in the 66 patients treated with one course Cayston 75 mg 3 times a day.

CP-AI-006 (long term study)

CP-AI-006 was an open-label follow-on study to CP-AI-005 and CP-AI-007 evaluating the safety of repeated exposure to Cayston and the effect on disease-related endpoints over multiple 28-day courses. Patients received Cayston at the same frequency (2 or 3 times a day) as they took Cayston or placebo in the randomised studies. Patients continued on their baseline medications and whenever indicated additional antibiotics were used in the majority of patients to treat exacerbations. Each 28-day course of Cayston was followed by a 28-day off drug period. Over nine 28-day courses of therapy, measures of pulmonary function (FEV_1), CFQ-R respiratory symptoms scores, and *P. aeruginosa* sputum density showed a trend to improvement while the patients were on treatment compared with off treatment. However, due to the uncontrolled nature of the study and concomitant medications no conclusion can be drawn on the sustainability of the observed short term benefit over subsequent courses of treatment.

Review of Efficacy Results in Paediatric patients

In total, 179 unique paediatric patients (49 subjects aged 6 to 12 years, 130 subjects aged 13 to 17 years) have received AZLI in these trials (Table 2). The numbers of paediatric patients included in each efficacy study are summarized below. The reported efficacy results are reported in table 3a-3c.

Table 2: Paediatric patients Included in Completed Phase 2/3 Clinical Studies of AZLI

	Children (6-12 years)	**Adolescents (13-17 years)**	**Total Paediatrics (6-17 years)**
Short-Term Studies			
Study CP-AI-003	0	27 (21 AZLI)	27 (21 AZLI)
Study CP-AI-005	10 (9 AZLI)	36 (25 AZLI)	46 (34 AZLI)
Study CP-AI-007	15 (11 AZLI)	22 (10 AZLI)	37 (21 AZLI)
Study GS-US-205-0117	32 (14 AZLI)	57 (28 AZLI)	89 (42 AZLI)

Long-Term Studies			
Study CP-AI-006[a]	18 (18 AZLI)	37 (37 AZLI)	55 (55 AZLI)
Study GS-US-205-0110[b]	13 (8 AZLI)	46 (20 AZLI)	59 (28 AZLI)
Total Number of Subjects Studied	**88**	**225**	**313**
Total Number of Subjects Treated with AZLI	**62**	**153**	**215**
Total Number of Unique Subjects Treated with AZLI [a]	**49**	**130**	**179**
Total Number of Unique Subjects Treated with AZLI in Long-Term Studies	**28**	**68**	**96**

a Note, subjects may have participated in more than one study. For example, subjects treated with AZLI in Study CP-AI-006 previously participated in either placebo-controlled study CP-AI-005 or CP-AI-007. Thus, the total number of unique paediatric patients exposed to AZLI was 179 subjects (49 children, 130 adolescents).

b Includes randomised and extension phases.

Table 3a: Efficacy results from AZLI 75 mg TID studies in paediatric patients (6-12 years)

study	CP-AI-003[#]	CP-AI-005		CP-AI-007		CP-AI-006	US-GS-205-0110		US-GS-205-0117		US-GS-205-0111[@]
	AZLI	**placebo**	**AZLI**	**placebo**	**AZLI**	**AZLI**	**TNS**	**AZLI**	**placebo**	**AZLI**	**AZLI**
N	0	1	5	4	11	18	5	8	25	22	26
FEV_1 (L), adjusted mean % change from baseline	**-**	**-**	**-**	**-8.2**	**3.0**	**?**	**-**	**-**	**-**	**-**	**-**
CFQ-R RSS, mean change from baseline	**-**	**-**	**-**	**0.00**	**15.00**	**-**	**-**	**-**	**-**	**-**	**-**
Log_{10} PA CFU/g, change	**-**	**-**	**-**	**-**	**-**	**0.47[$]**	**-3.228**	**-3.487**	**0.46**	**-0.29**	**-**

in the dose finding study CP-AI-003 only BID treatment was used.

$ Log_{10} PA observed end of treatment course 9 (18 months).

@ in study US-GS-205-0111 no efficacy data was measured.

Table 3b: Efficacy results from AZLI 75 mg TID studies in paediatric patients (13-17 years)

study	CP-AI-003[#]	CP-AI-005		CP-AI-007		CP-AI-006	US-GS-205-0110		US-GS-205-0117		US-GS-205-0111[@]
	AZLI	**placebo**	**AZLI**	**placebo**	**AZLI**	**AZLI**	**TNS**	**AZLI**	**placebo**	**AZLI**	**AZLI**
N		11	12[%]	12	10	37	16	20	22	20	83
FEV_1 (L), adjusted mean % change from baseline	**-**	**-**	**-**	**-5.4**	**8**	**?**	**-**	**-**	**-**	**-**	**-**
CFQ-R RSS, mean change from baseline	**-**	**-**	**-**	**-8.56**	**16.67**	**-**	**-**	**-**	**-**	**-**	**-**
Log_{10} PA CFU/g, change	**-**	**-**	**-**			**-0.13[4]**	**0.053**	**-0.482**	**-0.01**	**-2.05**	**-**

in the dose finding study CP-AI-003 only BID treatment was used.

$ Log_{10} PA observed end of treatment course 9 (18 months).

@ in study US-GS-205-0111 no efficacy data was measured

Table 3c: Efficacy results from AZLI 75 mg TID studies in paediatric patients (<18 years)

study	CP-AI-003[#]	CP-AI-005		CP-AI-007		CP-AI-006	US-GS-205-0110		US-GS-205-0117		US-GS-205-0111[@]
	AZLI	**placebo**	**AZLI**	**placebo**	**AZLI**	**AZLI**	**TNS**	**AZLI**	**placebo**	**AZLI**	**AZLI**
N	-	-	-	-	-	-	31	28	47	42	**-**
FEV_1 (L), adjusted mean % change from baseline	**-**	**-**	**-**	**--**	**-**	**?**	**2.80 (3.28)**	**9.08 (3.37)**	**-**	**-**	**-**
CFQ-R RSS, mean change from baseline	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Log_{10} PA CFU/g, change	**Treatment difference compared to placebo -1.6**	**-**	**-**	**-**	**-**	**-**	**-0.505**	**-0.854**	**0.21**	**-1.32**	**-**

in the dose finding study CP-AI-003 only BID treatment was used.

@ in study US-GS-205-0111 no efficacy data was measured

Dose finding and short term studies

Study CP-AI-003

Study CP-AI-003 enrolled 27 (26%) paediatric patients (13 to 17 years old). Overall, 6 paediatric patients were treated with placebo, 9 were treated with 75 mg AZLI twice daily (BID), and 12 were treated with 225 mg AZLI BID. Among the 27 paediatric patients, 4 subjects had baseline FEV_1 < 75% predicted and 23 subjects had baseline FEV_1 ≥ 75% predicted.

Among paediatric patients, there was a mean increase in percent change in FEV_1 from Day 0 to Day 14 in the AZLI treatment groups and a slight decline in the placebo group (-1.2% in the placebo group, 9.1% in the 75 mg AZLI BID group, and 3.4% in the 225 mg AZLI BID group).

A statistically significant mean reduction in $\log_{10}$ *PA* CFU/g was observed in the overall study population in both AZLI treatment groups compared with placebo following a 14-day treatment course. At Day 14, the mean (confidence interval [CI]; p-value) difference between AZLI and placebo in change in $\log_{10}$ *PA* CFU/g was -1.6 (-2.4, -0.7; p = 0.0005) for the 75 mg AZLI group and -2.3 (-3.2, -1.5; p < 0.0001) for the 225 mg AZLI group.

Comment:

Study CP-AI-003 was a dose finding 75 mg AZLI BID versus 225 mg AZLI BID. The ITT population included 105 patients of which only 9 paediatric patients (13-17 years; none in the age group 6-12 years) were treated with AZLI 75 mg BID. Compared to placebo this group showed a mean percentage change in FEV_1 from Day 0 to Day 14 of -1.2% in the placebo group and 9.1% in the 75 mg AZLI BID group. In the total paediatric population, 4 subjects had baseline FEV_1 < 75% predicted and 23 subjects had baseline FEV_1 ≥ 75% predicted.

At Day 14, the mean difference between AZLI and placebo in change in $\log_{10}$ PA CFU/g was -1.6 (CI; -2.4, -0.7; p = 0.0005) for the 75 mg AZLI BID group.

However, as this study was not conducted with the final dose of 75mg TID this study does not contribute to the evaluation the efficacy of the approved 75 mg AZLI TID dosage for Cayston.

Study CP-AI-005

In study CP-AI-005, 211 subjects completed the 28-day TNS run-in period and were treated with 75 mg AZLI BID, 75 mg AZLI TID, or placebo. Study CP-AI-005 enrolled 46 (21.8%) paediatric patients (10 [4.7%] aged 6 to 12 years, 36 [17.1%] aged 13 to 17 years). Overall, 12 paediatric patients were treated with placebo (1 aged 6 to 12 years, 11 aged 13 to 17 years), 17 were treated with 75 mg AZLI BID (4 aged 6 to 12 years, 13 aged 13 to 17 years), and 17 were treated with 75 mg AZLI TID (5 aged 6 to 12 years, 12 aged 13 to 17 years).

The primary endpoint was time to need for IV or inhaled anti-PA antibiotics other than trial drug with documented symptom(s) predictive of pulmonary exacerbation (such as decreased exercise tolerance, increased cough, increased sputum/chest congestion, decreased appetite) following start of blinded study drug. If the patient needed inhaled or IV antibiotics for at least one of the reasons above, he/she was withdrawn from the trial. If at least one of thee four symptoms was present, he/she was considered an event patient for the primary analysis.

There were only 10 subjects between the ages of 6 and 12 years in Study CP-AI-005, so analyses of treatments within this youngest subgroup were not feasible. The proportion of subjects under 18 years of age who required inhaled or IV antibiotics was lower than that of subjects aged 18 years or older. In both age subgroups, the proportion of subjects in the pooled AZLI group who required inhaled or IV antibiotics was lower than that of subjects in the pooled placebo group (<18 years of age: 9/34 [26%] pooled AZLI vs. 5/12 [42%] pooled placebo; ≥ 18 years of age: 34/101 [34%] pooled AZLI vs. 33/64

[52%] pooled placebo). Among those subjects 18 years of age or older, the time to need for inhaled or IV antibiotics was prolonged for the pooled AZLI treatment group compared to the pooled placebo group, and this difference was statistically significant (p = 0.0207). In the subgroup of subjects < 18 years of age, the difference was not statistically significant, but was of a similar magnitude to that seen in subjects 18 years of age or older.

Comment:

In the double blind, placebo controlled study CP-AI-005, 211 subjects completing a **28-day TNS run-in period** were randomised to 75 mg AZLI BID, 75 mg AZLI TID, or placebo. The primary endpoint was time to need for intravenous or inhaled antipseudomonal antibiotics. Secondary endpoints were e.g. FEV_1% and CFQ-R. This study enrolled **46** (21.8%) paediatric patients (**10** [4.7%] aged 6 to 12 years, **36** [17.1%] aged 13 to 17 years). Overall, 17 were treated with selected dose of 75 mg AZLI TID (5 aged 6 to 12 years, 12 aged 13 to 17 years).

In the original MAA, data per subgroup was provided.

In both age subgroups, the proportion of subjects in the pooled AZLI group who required inhaled or IV antibiotics was lower than that of subjects in the pooled placebo group. In patients <18 years of age this was 9/34 [26%] for the pooled AZLI vs. 5/12 [42%] in the placebo group. In the subgroup of subjects <18 years of age, there was no significant difference in time to need for inhaled or IV antibiotics between pooled AZLI and placebo, a similar trend was observed as seen in subjects 18 years of age or older. This might be due to less compromised lung function or better physical condition of paediatric patients.

Study CP-AI-007

In study CP-AI-007, overall 164 subjects were treated with 75 mg AZLI TID or placebo. In this study 37 (22.5%) paediatric patients (15 [9.1%] aged 6 to 12 years, 22 [13.4%] aged 13 to 17 years) were enrolled. Overall, 16 paediatric patients were treated with placebo (4 aged 6 to 12 years, 12 aged 13 to 17 years) and 21 were treated with 75 mg AZLI TID (11 aged 6 to 12 years, 10 aged 13 to 17 years).

The primary endpoint was change from Day 0 (baseline) to Day 28 in clinical symptoms as assessed by the respiratory domain of the CFQ R. The CFQ-R was administered at Days 0, 14, 28, and 42/Early Termination in a similar fashion as in study CP-AI-005.

Efficacy subgroup analyses by age group were conducted for FEV_1 and CFQ-R RSS. Although statistically significant improvement in children was not demonstrated due to the small sample size, robust clinical significance was observed and the magnitude of improvement among children was greater than that seen among adults. Data are presented for 3 age groups, 6 to 12 years, 13 to 17 years, and ≥ 18 years, in Table 4.

Table 4: Change at Day 28 from Baseline in FEV_1 and CFQ-R RSS by Age Group: Study CP-AI-007

	Children (6-12 years)		Adolescents (13-17 years)		Adults (≥ 18 years)	
	Placebo	AZLI	Placebo	AZLI	Placebo	AZLI
FEV_1 (L), adjusted mean % change from baseline	-8.2	3.0	-5.4	8	-2.4	**8**
Number of subjects with available data	**4**	**11**	**12**	**10**	**68**	**58**
CFQ-R RSS, mean change from baseline	0.00	15.40	-8.56	16.67	-0.83	**4.99**
Number of subjects with available data	**4**	**11**	**12**	**10**	**67**	**59**

Comment:

Study CP-AI-007 was a placebo controlled double blind trial. This study was already discussed during the initial Marketing Authorisation Application. The study included in total 164 subjects of which 16 paediatric patients were treated with placebo (4 aged 6 to 12 years, 12 aged 13 to 17 years) and 21 were treated with 75 mg AZLI TID (11 aged 6 to 12 years, 10 aged 13 to 17 years).

In the **overall population** the adjusted mean percent change in FEV_1 from baseline at Day 28 (adjusted for disease status and baseline value) was 7.9% for AZLI-treated subjects and -2.4% for placebo-treated subjects versus placebo. The treatment difference of 10.3% reflected a clinically significant improvement in pulmonary function. The percent of subjects who used any antipseudomonal antibiotics was higher in the placebo group (36%) compared with the AZLI group (18%), and this difference was statistically significant. Also there was a trend towards more subjects being hospitalized from Day 0 to 42 in the placebo group than in the AZLI group: 4 subjects (5.0%) were hospitalized in the AZLI group compared with 12 subjects (14%) in the placebo group. In addition to fewer hospitalizations, the mean number of hospitalization days was lower for subjects in the AZLI group than in the placebo group

In the **paediatric subpopulation** there is lack in power to detect significant differences due to the small numbers. However with respect to FEV_1 and CFQ-R RSS a similar trend is observed as in adults.

It is noted that in table 4 in the subheading "CFQ-R RSS" the numbers of patients in the column "adults" report different patient number compared to the subheading "FEV_1".

Integrated Studies CP-AI-007 and CP-AI-005

Subgroup analyses of the efficacy endpoints (FEV_1 and CFQ-R RSS) were conducted for subjects aged 6 to 12 years, 13 to 17 years, < 18 years and ≥ 18 years in a pooled analysis of the Phase 3 placebo-controlled registration studies (Table 3). Despite robust clinical significance, where the magnitude of improvement was greater than that seen in adults, the small number of paediatric patients precluded the ability to demonstrate statistically significant improvement in children (aged 6-12 years); however, statistically significant improvements were demonstrated for FEV_1 and CFQ-R RSS in the adolescent subgroup (table 5).

There was a significant treatment difference for change in $\log_{10}$ *PA* CFU/g sputum between the AZLI TID and placebo groups only for adult subjects (≥ 18 years old) following a 28-day treatment course

(treatment difference: -0.795, p = 0.0001); change in $\log_{10}$ *PA* CFU/g approached significance for paediatric patients < 18 years old (treatment difference: -1.213, p = 0.0824); treatment differences in the paediatric patients 6 to 12 and 13 to 17 were -2.173 and -0.824, respectively. Although the treatment differences did not reach statistical significance for younger subjects (< 18 years), AZLI-treated subjects in these subgroups demonstrated greater CFU reductions than adults (≥ 18 years). This apparent discrepancy may be due to the small number of paediatric patients and/or the decrease in sputum *PA* density observed among placebo-treated subjects < 18 years old which is in contrast to the increase in sputum *PA* density observed among adult placebo-treated subjects.

Table 5: Change at Day 28 from Baseline in FEV_1 and CFQ-R RSS by Age Group: Integrated Studies CP-AI-007 and CP-AI-005

Change at Day 28 from Baseline (Day 0)		Children (6-12 years)		Adolescents (13-17 years)		Adults (≥ 18 years)	
		Placebo (N = 5)	AZLI (N = 20)	Placebo (N = 23)	AZLI (N = 35)	Placebo (N = 132)	AZLI (N = 160)
FEV_1 (L), % change	Mean	1.3	5.8	-5.1	7.3	-1.8	5.2
	Tx effect (p-value)	4.5 (0.6488)		12.4 (0.0035)		7.0 (< 0.0001)	
CFQ-R RSS, change	Mean	1.7	8.9	-5.2	7.8	-0.6	4.7
	Tx effect (p-value)	7.2 (0.2626)		13.0 (0.0009)		5.3 (0.0078)	
Log_{10} *PA* CFU/g, change	Mean	0.0	-1.9	-0.3	-1.1	0.2	-0.6
	Tx effect (p-value)	-1.9 (0.3624)		-0.8 (0.1566)		-0.8 (< 0.0001)	

Note: Adjusted means and p-values from Analysis of Covariance with treatment as a fixed effect and baseline value as a covariate. Data from both the BID and TID treated patients were taken into account.

Comment:

In order to increase power to detect any significance the MAH pooled the paediatric patients from both studies CP-AI-005 and CP-AI-007. It should be noted that in study CP-AI-005 4 subjects (aged 6-12 years; 4/20=20%) and 13 subjects (13-17 years; 13/35=37.1%) received 75 mg AZLI **BID** treatment. These BID-treated patients were included as well in the pooled dataset. Moreover in study CP-AI-005 patients received a 28 day run-in treatment with TNS, whilst in study CP-AI-007 patients did not. To support the final dose recommendation of 75 mg TID only data of children with this dosing scheme is of interest. However, further breakdown of this population to even smaller subgroups will not reveal any meaningful results because of lack of power. Generally it is questionable whether any further placebo controlled data will add relevant information, since a differential effect on FEV_1 by suppression of chronic infection of Pseudomonas most likely will appear.

It appears that in the paediatric subpopulations a similar trend in FEV_1 and CFQ-R is observed as seen in the adult population, which appears to be more pronounced in the 13-17 year old subjects. However this result might be overestimated as these studies included both the BID and TID treated AZLI patients.

Note that in the reduction of $\log_{10}$ PA CFU/g sputum data as presented in table 5 above includes the **BID**- and **TID-**treated patients as well. In the clinical-microbiology summary, the reduction of $\log_{10}$ PA

CFU/g sputum for the TID-treated patients are presented only. Treatment differences in the paediatric patients 6 to 12 and 13 to 17 were -2.173 and -0.824, respectively, however non-significant (in contrast to the adult patients).

Study GS-US-205-0117

In Study GS-US-205-0117, 157 subjects were treated with 75 mg AZLI TID or placebo. This study enrolled 89 (56.7%) paediatric patients (47 [29.9%] aged 6 to 13 years, 42 [26.8%] aged 14 to 17 years).

This study enrolled subjects with CF and chronic PA infection at high risk for disease progression, which included those with moderate to severe lung function impairment and limited treatment options and those who had completed participation in Study CP AI 006. Study GS-US-205-0117 **did not meet its primary endpoint of change in CFQ-R RSS at Day 28 from Day 0**. In the overall study population, AZLI-treated subjects did not demonstrate clinically significant improvement in CFQ-R RSS, although there was an overall improvement in scores.

No statistically significant differences in respiratory symptoms (as measured by the CFQ-R RSS) were observed between treatment groups for paediatric or adult subjects. There was a greater improvement in the CFQ-R RSS for adults (≥ 18 years) than for paediatric patients (< 18 years). At Day 28, adult subjects (aged ≥ 18 years; n = 68: 34 AZLI and 34 placebo) showed an adjusted mean change of 5.11 on AZLI compared with 0.44 on placebo for the CFQ-R RSS scores (treatment effect: 4.67; p = 0.183). The adjusted mean change for younger subjects (aged < 18 years; n = 87: 41 AZLI and 46 placebo) was 1.54 on AZLI and 1.77 on placebo (treatment effect: -0.23; p = 0.942).

Among children (aged 6 to 13 years), adjusted mean change (log_{10} CFU/g) at Day 28 was -0.29 on AZLI compared with 0.46 on placebo (treatment effect: -0.76; p = 0.556), and among adolescents (aged 14 to 17 years), adjusted mean change at Day 28 was -2.05 on AZLI compared with -0.01 on placebo (treatment effect: -2.03; p = 0.082). In adults no significance could be shown, although a treatment effect was present (-0.92; p=0.125). The smaller sample size in each subgroup may explain the lack of statistical significance.

Table 6: Change in Log10 PA CFU/g Sputum from Baseline by Age Group: Study GS-US-205-0117

		Mean (SD)	Adjusted mean	Treatment difference	95% CI (p-value)
Children (6-13 years)[a]	Placebo (n=9)	0.45 (3.10)	0.46	-0.76	-3.47, 1.96 (0.556)
	AZLI (n=6)	-0.27 (1.56)	-0.29		
Children (14-17 years	Placebo n=9)	-0.08 (2.26)	-0.01	-2.03	-4.35, 0.29 (0.082)
	AZLI (n=9)	-1.98 (2.33)	-2.05		
Children (6-17 years)	Placebo (n=18)	0.19 (2.65)	0.21	-1.53	-3.15, 0.09 (0.063)
	AZLI (n=15)	-1.30 (2.17)	-1.32		
Adults (≥18 years)	Placebo (n=13)	-0.43 (1.18)	-0.41	-0.92	-2.11, 0.27 (0.125)

	AZLI (n=34)	-1.33 (1.87)	-1.33		

a The age ranges used in GS-US-205-0117 are different from those in other studies because the age ranges coincide with those of the CFQ-R, which was the primary endpoint for this study.

Comment:

In double blind, placebo controlled study GS-US-205-0117, 157 subjects were treated with 75 mg AZLI TID or placebo. This study enrolled 89 (56.7%) paediatric patients (47 [29.9%] aged 6 to 13 years, 42 [26.8%] aged 14 to 17 years). **NOTE:** Inclusion criteria >75% FEV_1, which is different compared to the other studies (FEV_1 ≥25% ≤75%)

Study GS-US-205-0117 was already assessed within the context of Specific Obligation SO2 (AR dated February 2010). The primary objective of Study GS-US-205-0117 was to assess the safety and efficacy of a 28 day course of AZLI in patients with CF, mild lung disease (forced expiratory volume in 1 second [FEV1] > 75% predicted), and chronic PA infection of the lung. This population is significantly different from the populations in the other controlled trials. The modest effect seen with AZLI in this study is most probably due to the high baseline value of FEV_1 % predicted (95.1%). Lung function is considered normal by the CF Foundation if FEV_1 > 90% predicted.

This study did **not** meet its primary endpoint of change in CFQ-R RSS at Day 28 from Day 0 in the overall population. Also in **the paediatric subpopulation,** AZLI-treated subjects did not demonstrate clinically significant improvement in CFQ-R RSS as well. Data on FEV_1 % was not provide for paediatric patients. It must be borne in mind that the usefulness of CFQ-R as a primary endpoint in confirmatory clinical trials is not sufficiently validated as discussed in earlier assessments of the original registrational studies for Cayston.

Although the reduction in Log_{10} PA CFU/g sputum for AZLI- versus placebo-treated subjects was statistically significant for the overall population (treatment difference: -1.21, p = 0.016), in **the paediatric subpopulations** (6-12 years and 13-17 years) and the adult population (≥18 years), however, this was not achieved.

Long term studies

Study CP-AI-006

Study CP-AI-006 was an open-label follow-on study to CP-AI-005 and CP-AI-007 evaluating the safety of repeated exposure to Cayston and the effect on disease-related endpoints over **nine** 28-day courses. Patients received Cayston at the same frequency (2 or 3 times a day) as they took Cayston or placebo in the randomised studies. **Patients continued on their baseline medications and whenever indicated, additional antibiotics were used in the majority of patients to treat exacerbations.** Each 28-day course of Cayston was followed by a 28-day off drug period. In Study CP-AI-006, patients were allowed to be treated as needed with any antipseudomonal antibiotics other than IV aztreonam therapy.

Study CP-AI-006 was designed to assess the long term safety of AZLI (over 9 courses of treatment), with primary endpoints being adverse events, airway reactivity, vital signs and laboratory analyses.

Study CP-AI-006 enrolled 274 subjects, 85 on AZLI BID and 189 on AZLI TID. Study CP-AI-006 enrolled 55 (20.1%) paediatric patients (18 [6.6%] aged 6 to 12 years, 37 [13.5%] aged 13 to 17 years). Overall, 19 were treated with 75 mg AZLI BID (4 aged 6 to 12 years, 15 aged 13 to 17 years) and 36 were treated with 75 mg AZLI TID (14 aged 6 to 12 years, 22 aged 13 to 17 years).

For subjects <18 years of age who received 75 mg AZLI TID, the mean percent change in FEV_1 of predicted was positive at the end of every on-treatment interval and negative at the end of every off-treatment interval (with the exception of the end of Treatment Course 7 [Visit 13] and the start of Treatment Courses 3 and 8, respectively). Overall, the mean percent change from baseline in FEV_1 percent of predicted at the end of each on-treatment interval was greater in subjects ≥18 years of age than subjects <18 years of age.

Decreases from baseline in $\log_{10}$ *PA* CFU/g sputum were observed in the **overall study population** over the 9 treatment courses (28 days on treatment followed by 28 days off treatment) in both the AZLI BID and TID groups. The mean changes at the end of each treatment course were generally greater for subjects in the AZLI TID group relative to the AZLI BID group.

Mean *PA* CFU changes in sputum for children treated with AZLI TID, aged **6 to 12 years** old (N= 14), were similar in magnitude and direction to those of adults; mean decreases from baseline (-0.29 to -1.69 $\log_{10}$ CFU/g) in sputum *PA* density following 28 days of AZLI were generally observed. Unlike the adult population, no changes or increases in sputum *PA* density were generally observed at the end of off AZLI periods in the AZLI TID paediatric patients aged 6 to 12 years old.

Mean *PA* CFU changes in sputum for adolescents treated with AZLI TID, aged **13 to 17 years** old (n=22), were similar in magnitude and direction to those for adults; mean decreases from baseline (-0.13 to -0.75 $\log_{10}$ CFU/g) in sputum *PA* density following 28 days of AZLI were generally observed. Similar to adult subjects and indicative of continuous *PA* suppression, mean decreases from baseline in sputum PA density at the end of off AZLI periods were generally observed.

Table 7: Change (SD) Log10 PA CFU/g Sputum, Treatment Courses 1 to 9: Children, Adolescents and Adults

Treatment Course	AZLI TID Children 6 to 12 years (N = 14)	AZLI TID Adolescents 13 to 17 years (N = 22)	AZLI TID Adults ≥ 18 years (N = 153)
End Treatment Course 1 (Visit 2)			
n	7	17	105
Mean (SD)	-0.44 (1.110)	-0.53 (2.301)	-0.88 (1.708)
Start Treatment Course 2 (Visit 3)			
n	8	16	109
Mean (SD)	0.02 (1.442)	-1.11 (2.700)	-0.18 (1.623)
End Treatment Course 2 (Visit 4)			
n	9	13	102
Mean (SD)	-1.69 (2.476)	-0.75 (2.928)	-0.74 (2.088)
Start Treatment Course 3 (Visit 5)			
n	9	13	105
Mean (SD)	0.02 (3.126)	-0.65 (1.776)	-0.04 (1.547)
End Treatment Course 3 (Visit 6)			
n	7	14	90
Mean (SD)	-0.30 (0.806)	-0.40 (2.591)	-0.57 (2.128)
Start Treatment Course 4 (Visit 7/8)			
n	9	12	94
Mean (SD)	0.65 (0.877)	-0.74 (2.410)	-0.05 (1.798)
End Treatment Course 4 (Visit 9)			
n	6	12	88
Mean (SD)	-0.65 (0.668)	-0.73 (2.763)	-0.73 (2.111)
Start Treatment Course 5 (Visit 10)			
n	8	10	95
Mean (SD)	-0.02 (0.837)	0.12 (1.173)	-0.39 (1.859)
End Treatment Course 5 (Visit 11)			
n	8	10	86
Mean (SD)	-0.89 (2.696)	-0.24 (2.360)	-0.53 (1.847)
Start Treatment Course 6 (Visit 12)			
n	6	11	83
Mean (SD)	1.15 (1.873)	-0.15 (0.899)	-0.36 (1.915)

Treatment Course	AZLI TID Children 6 to 12 years (N = 14)	AZLI TID Adolescents 13 to 17 years (N = 22)	AZLI TID Adults ≥ 18 years (N = 153)
End Treatment Course 6 (Visit 13)			
n	4	11	71
Mean (SD)	-0.29 (0.469)	0.38 (1.470)	-0.70 (2.086)
Start Treatment Course 7 (Visit 14)			
n	6	10	76
Mean (SD)	0.76 (0.889)	0.34 (1.253)	-0.46 (2.095)
End Treatment Course 7 (Visit 15)			
n	5	12	75
Mean (SD)	-0.46 (1.879)	0.45 (1.895)	-0.92 (2.320)
Start Treatment Course 8 (Visit 16)			
n	6	9	78
Mean (SD)	0.05 (0.861)	-1.33 (2.412)	-0.22 (2.049)
End Treatment Course 8 (Visit 17)			
n	5	11	73
Mean (SD)	0.13 (0.534)	-0.58 (2.692)	-0.80 (2.150)
Start Treatment Course 9 (Visit 18)			
n	5	11	70
Mean (SD)	0.61 (0.722)	-0.39 (1.087)	-0.53 (1.948)
End Treatment Course 9 (Visit 19)			
n	5	11	69
Mean (SD)	0.47 (1.074)	-0.13 (1.853)	-0.75 (2.133)
Follow-up (Visit 20)			
n	5	9	72
Mean (SD)	1.09 (0.541)	-0.63 (0.857)	-0.57 (2.398)

Comment:

CP-AI-006 was a long-term open-label follow-on study to CP-AI-005 and CP-AI-007 evaluating the safety and tolerabilty of repeated exposure to Cayston and the effect on disease-related endpoints over multiple 28-day courses. This study was already extensively discussed in the original MAA. The patients from study CP-AI-007 did not have a run-in treatment. Patients received Cayston at the same frequency (2 or 3 times a day) as they took Cayston or placebo in the randomised studies. Patients continued on their baseline medications and whenever indicated additional antibiotics were used in the majority of patients to treat exacerbations. Each 28-day course of Cayston was followed by a 28-day off drug period.

It is noticed that in the paediatric subgroup 6 to 12 years old from the end of course 8 no reduction in Log_{10} PA sputum is observed. Whereas in the subpopulation 13 to 17 years old it appears to show the same trend as in adults, although at course 5 to 7, it appears that AZLI treatment had no effect on the reduction of PA in sputum.

This open uncontrolled follow-on study provides some insight into the long term effect, and particularly raises some concern with regard to the potential decrease in efficacy, especially in the youngest age groups. Comparative data are needed to ascertain whether this is different from other PA treatments.

Study GS-US-205-0110

In long term follow up study GS-US-205-0110, a subpopulation of 28 paediatric patients were treated with 75 mg AZLI TID (8 subjects aged 6 to 12 years; 20 subjects aged 13 to 17 years) and 31 were treated with TNS (5 subjects aged 6 to 12 years; 26 subjects aged 13 to 17 years) during the randomised phase. Demographic and baseline characteristics were generally balanced between treatment and age stratified groups. Statistically significant differences between treatment groups were noted in the CFQ-R RSS score for the ≥ 18 years subgroup. The mean baseline CFQ-R RSS score was higher for subjects ≥ 18 years treated with AZLI than for subjects ≥ 18 years treated with TNS.

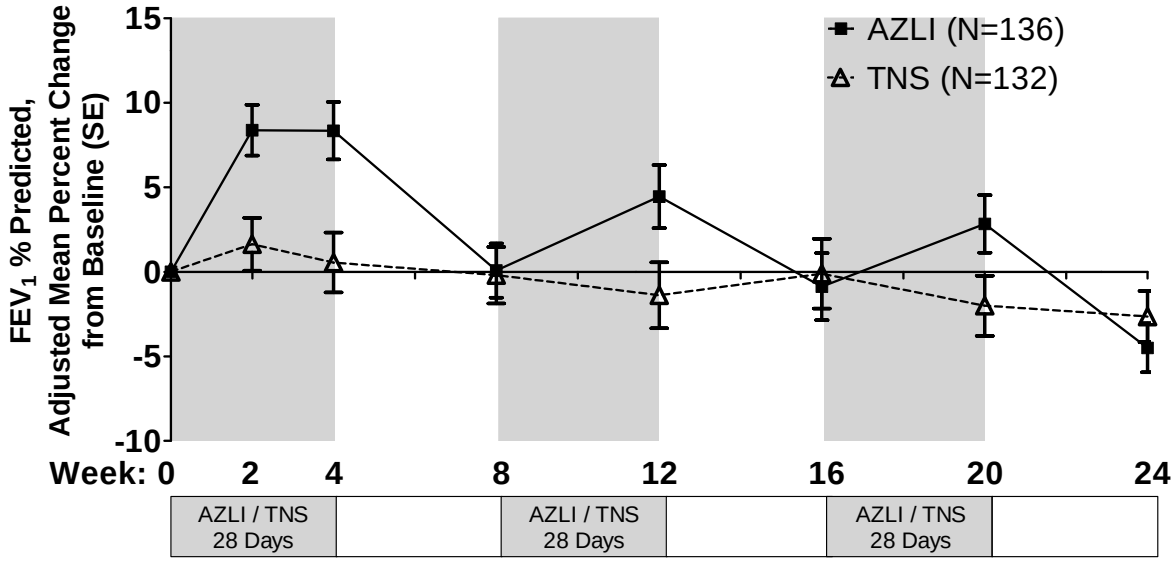
Subjects <18 years had higher baseline FEV_1 % predicted and CFQ-R RSS score and lower log_{10} *PA* CFU compared to subjects ≥ 18 years (<18 years Log_{10} PA sputum 5.11 (sd 2.97); ≥18 years Log_{10} PA sputum 6.68 (sd 1.69)). Mean (SD) FEV_1 % predicted for subjects < 18 years was 56.32 (14.19) compared to 51.15 (15.13) for subjects ≥ 18 years.

Study GS-US-205-0110 is a long-term, double blind, active controlled, safety/efficacy study comparing AZLI with TNS. This study was critically discussed in the SO2 and renewal procedure R-15 with respect to the adult data. Main points of criticism were the lack of benefit of ALZI in CF patients who had received minimal pre-treatment with TNS before inclusion in the trial, the increase in resistance to aztreonam and disagreement on possible superiority claims based on 3 months data.

Analysis of FEV_1 % Predicted Change from Baseline at Day 28 and Across 3 Courses of Treatment

Subjects < 18 years treated with AZLI showed improvement in lung function by Day 28 that was statistically non-inferior to TNS-treated subjects. The adjusted mean (SE) relative change from baseline in FEV_1 % predicted at Day 28 based on LOCF imputed data was 9.08 (3.37) for subjects treated with AZLI compared to 2.80 (3.28) for subjects treated with TNS; the treatment difference of -6.28 was not statistically significant (95% CI: -13.8, 1.2; p-value: 0.0982). The magnitude of relative change in FEV_1 % predicted in paediatric patients treated with AZLI was numerically greater compared to adult subjects treated with AZLI.

Figure 1: Relative Change in FEV_1 % Predicted from Baseline on Imputed Data by LOCF: Study GS-US-205-0110



Subjects < 18 years treated with AZLI also showed improvement in lung function across 3 treatment courses that was greater than TNS-treated subjects, although no statistical differences were detected between treatment groups. The adjusted mean (SE) actual change from baseline in FEV_1 % predicted across 3 treatment courses for this age group was 2.23 (1.73) for subjects treated with AZLI and 0.10 (1.67) for subjects treated with TNS (treatment difference: -2.14, p-value: 0.3085). The magnitudes of change in paediatric patients were similar to those seen in adult subjects, but the small number of paediatrics limits the ability to detect statistical differences.

Comment:

Based on tables below it is shown that the treatment effect of AZLI versus TNS in paediatric patients (<18 years) follows the same trend as in adults over 3 courses (treatment difference -2.14 versus -2.98) in favour of AZLI over TNS. AZLI was non-inferior compared to TNS in both adults and children. The same effect is observed at day 28. This might be due to the small paediatric population and thus there is lack of power to detect any significance.

Table 8: **21 GS-US-205-0110 Randomized Phase: Primary Non-inferiority and Superiority Analyses by Age Group (ITT Population)**

Endpoint	Statistic	< 18 years		≥ 18 years	
		AZLI (N = 28)	TNS (N = 31)	AZLI (N = 108)	TNS (N = 101)
Relative Change from Baseline in FEV_1 % Predicted at Day 28 (Week 4)	n	28	31	108	101
	Adj mean (SE) [a]	9.08 (3.37)	2.80 (3.28)	8.38 (1.96)	-0.60 (2.07)
	Treatment Difference	-6.28		-8.44	
	95% CI	-13.76, 1.20		-13.04, -3.84	
	95% Upper boundary < 4 (noninferiority)	yes		yes	
	p-value (superiority)	0.0982		0.0004	
Average of Actual Change in FEV_1 % Predicted at Visits 4, 6, and 8	Adj mean (SE) [b]	2.23 (1.73)	0.10 (1.67)	2.30 (0.73)	-0.67 (0.77)
	Treatment Difference	-2.14		-2.98	
	p-value	0.3085		0.0020	

Adjusted means from model including treatment, Visit 2 FEV_1 % predicted, and previous inhaled tobramycin use.

LOCF method is used to impute missing data for statistical analyses.

a Comparisons are made based on type III sum of squares ANCOVA models.

b Adjusted means from MMRM model including treatment, Visit 2 FEV_1 % predicted, previous inhaled tobramycin use, visit, treatment, and treatment/visit interaction for all subjects.

Source: Section 15.1, Tables 14.2.1.2.9 and 14.2.1.2.10; Appendix 16.2, Listing 16.2.6.1.2

Figure 1 shows the effect of AZLI versus TNS in the overall population. The treatment effect in FEV_1% is comparable in both adults and children, this applies to both AZLI treated as TNS treated patients. It is noticed that FEV_1% declines in the TNS-treated patients after one on-off cycle.

Time to Need for Antipseudomonal Antibiotics for Respiratory Events

The time to need for IV antipseudomonal antibiotics for a respiratory event by age group is presented in Table 9.

This endpoint was determined through the adjudication of events by a sponsor-independent, blinded review committee. There were no differences detected between AZLI and TNS-treated subjects < 18 years in the time to need for IV antipseudomonal antibiotic use for respiratory events. The median time to need for IV antibiotics for a respiratory event among these subjects was 177 days (i.e., ~6 months) for subjects treated with AZLI and was not estimable for subjects treated with TNS. Kaplan Meier event rates at Day 168 for respiratory hospitalizations were estimated as 43% and 39% for AZLI and TNS-treated subjects, respectively. The same number of subjects < 18 years treated with AZLI (11) experienced respiratory events requiring IV antipseudomonal antibiotics as subjects treated with TNS.

Table 9: GS-US-205-0110 Randomized Phase: Time to Need (Days) for IV Antibiotics for Respiratory Event by Age Group (ITT Population)

Statistic	< 18 years		≥ 18 years	
	AZLI (N = 28)	TNS (N = 31)	AZLI (N=108)	TNS (N=101)
Median	177	NE	NE	129
Min, Max	15, 177	1, NE	11, 169	3, 166
25th, 75th Percentiles	94, NE	103, NE	114, NE	36, NE
95% CI for Median	122, NE	115, NE	NE, NE	94, NE
Number of Subjects with an Event	13	13	36	56
Kaplan-Meier Event Rate at Day 168 (Week 24)	43%	39%	34%	58%
p-value[a]	0.7249		0.0003	

Kaplan-Meier method is used to calculate statistics for time to need for antipseudomonal antibiotics.

Antipseudomonal antibiotic use for respiratory event was determined through the adjudication of a sponsor-independent, blinded review committee.

NE – not estimable

All comparisons are made based on Log rank test.

Source: Section 15.1, Ad Hoc Request #4496 Table 2, and Ad Hoc Request #4559 Tables 4 and 5, Appendix 16.2, Listing 16.2.6.3.1

Time to First Respiratory Hospitalization

The median time to first hospitalization for a respiratory event by age group is presented in table 10. This endpoint was determined through the adjudication of events by a sponsor-independent, blinded review committee. No differences were detected between AZLI and TNS-treated subjects < 18 years in the time to first respiratory hospitalization. The median time to first hospitalization for a respiratory event among subjects < 18 years was not estimable for subjects treated with AZLI or TNS. Kaplan Meier event rates at Day 168 were estimated as 36% and 23% for AZLI and TNS-treated subjects, respectively. The number of subjects < 18 years with a respiratory related hospitalization was comparable between treatment groups with 10 subjects treated with AZLI and 8 subjects treated with TNS.

Table 10 GS-US-205-0110 Randomized Phase: Time to First Respiratory Hospitalization by Age Group (ITT Population)

Statistic	< 18 years		≥ 18 years	
	AZLI (N = 28)	TNS (N = 31)	AZLI (N = 108)	TNS (N =101)
Median	NE	NE	NE	NE
Min, Max	15, 122	6, 169	15, 169	5, 176
25th, 75th Percentile	94, NE	169, NE	NE, NE	108, NE
95% CI for Median	122, NE	NE, NE	NE, NE	NE, NE
Number of Subjects with an Event	10	8	22	33
Kaplan-Meier Event Rate at Day 168 (Week 24)	36%	23%	20%	34%
p-value[a]	0.3825		0.0217	

Kaplan-Meier method is used to calculate statistics for time to first respiratory hospitalization.

The respiratory hospitalization was determined through the adjudication of a sponsor-independent, blinded review committee.

NE – not estimable

a All comparisons are made based on Log rank test.

Source: Section 15.1, Ad Hoc Request #4497 Table 4 and Ad Hoc Request #4556, Tables 4 and 5, Appendix 16.2, Listing 16.2.6.4.2

Efficacy in Subjects Aged 6 to 12 Years and 13 to 17 Years

Subgroup analyses of the primary and key secondary efficacy endpoints were also conducted for subjects aged 6 to 12 years and 13 to 17 years (Table 11). None of the subgroup analyses reached statistical significance although some endpoints showed a favorable trend towards AZLI. Although time to need for IV antipseudomonal antibiotics suggested a benefit for AZLI there were no or only slight numerical differences between the group.

There were no 6-year-old subjects reported in the pivotal studies (CP-AI-005 and CP-AI-007); and only one 6-year-old subject (Subject 1401-640) was enrolled in Study GS-US-205-0110 and completed 3 courses of AZLI. The subject had improvement in lung function from baseline at all visits (Table 11).

Table 11: Primary and Key Secondary Endpoints for Subjects Aged 6 to 12 Years and 13 to 17 Years, Study GS-US-205-0110

Endpoint Age Group	Statistic	AZLI	TNS	Treatment Difference (TNS – AZLI)	p-value
Co-Primary (noninferiority): Relative Change from Baseline in FEV_1 % Predicted at Day 28					
Children (6-12 years)	**Adjusted mean (SE)[a]**	6.68 (7.12)	-1.70 (9.86)	-8.376	0.4568
	95% CI for treatment difference	---	---	-32.7, 16.0 Did not meet noninferiority margin of < 4%	---
Adolescents (13-17 years)	**Adjusted mean (SE)[a]**	10.70 (4.40)	4.50 (3.64)	-6.200	0.1546
	95% CI for treatment difference	---	---	-14.8, 2.4 Met noninferiority margin of < 4%	---
Co-Primary (superiority): Average of Actual Change of FEV_1 % Predicted at Visit 4, Visit 6, and Visit 8					
Children (6-12 years)	**Adjusted mean (SE)b**	-1.00 (3.26)	-12.60 (4.16)	-11.594	0.0541
Adolescents (13-17 years)	**Adjusted mean (SE)b**	4.245 (1.905)	1.679 (1.590)	-2.566	0.2034
Time to Need for IV Anti-*PA* Antibiotics for Respiratory Event					
Children (6-12 years)	**Median # of days (95% CI)**	177 (177, NE);	NE (40, NE);	NE	0.2690
	Kaplan Meier events rates at Day 168	13%	40%	-27%	
	Number of events	2	2	NA	
adolescents (13-17 years)	**Median # of days (95% CI)**	135 (90, NE)	NE (113, NE)	NE	0.3641
	Kaplan Meier events rates at Day 168	56%	39%	-17%	
	Number of events	11	11	NA	
Time to First Respiratory Hospitalization among All Subjects					
Children (6-12 years)	**Median # of days (95% CI)**	NE (NE, NE)	NE (NE, NE)	NE	0.4292
	Kaplan Meier events rates at Day 168	13%	0	13%	
	Number of events	1	0	NA	
Adolescents (13-17 years)	**Median # of days (95% CI)**	NE (90, NE)	NE (169, NE)	NE	0.2812
	Kaplan Meier events rates at Day 168	45%	27%	18%	
	Number of events	9	8	NA	

a Adjusted means from ANCOVA model including treatment, Visit 2 FEV_1 % predicted, and previous TNS use for all subjects in the subgroup

b Adjusted means from MMRM model including Visit 2 FEV1 % predicted, previous TNS use, treatment, visit, treatment and visit interaction for all subjects in the subgroup.

log_{10} PA CFU/g sputum

In the overall population, decreases in sputum *PA* density in subjects at the end of TNS therapy were smaller than decreases in subjects at the end of AZLI therapy but not significantly different. The adjusted mean (SE) change in sputum *PA* density for on-treatment visits was -0.55 (0.19) for subjects treated with AZLI and -0.32 (0.19) for subjects treated with TNS.

Table 12: GS-US-205-0110: Change from Baseline in Sputum Log_{10} *PA* CFU/g by Visit and Age, Randomised Phase

Visit	Statistics	< 18 years		≥ 18 years	
		AZLI TID (N = 28)	TNS (N = 31)	AZLI TID (N = 108)	TNS (N = 101)
Week 24 End of Off Treatment	n	13	20	73	63
	Adj mean (SE) [a]	0.063 (0.645)	0.389 (0.534)	-0.785 (0.295)	-0.760 (0.318)
	Trt diff	0.326		0.026	
	p-value	0.6066		0.9436	

Comment:

Based on the subpopulation analysis it is shown that the FEV_1% improves in both paediatric subpopulations compared to TNS. This effect is the same as seen in adults.

Based on the Kaplan Meier estimates at day 168 for Time to Need for IV Anti-PA Antibiotics for Respiratory Event (table 11), no difference was observed in the numbers of events between the AZLI and TNS treated paediatric patients. 6-12 years: ALZI 13% (n=2 events); TNS 40% (n=2 events). 13-17 years: ALZI 56% (n=11 events); TNS 39% (n=11 events). However in adults, AZLI was in favour over TNS (36 versus 56 events; table 8).

The Kaplan Meier event rates for Time to First Respiratory Hospitalization (table 11) suggest that AZLI-treated paediatric patients required more often hospitalisation. 6-12 years: ALZI 13% (n=1 event); TNS 0% (n=0 events). 13-17 years: ALZI 45% (n=9 events); TNS 27% (n=8 events). Interpretation should be done cautiously as only small numbers of paediatric patients were included. In adults, the number of events and the Time to first hospitalisation were significantly lower and longer, respectively, when ALZI was compared the TNS (22 versus 33 events) at day 168 (week 24), however these benefits can not be reproduced in younger patients.

Regarding the other tertiary (Change in weight/body mass index (BMI) at Week 20; Missed school/work days, Days 0 to 168; Treatment Satisfaction Questionnaire for Medication (TSQM) at Day 28 and either Day 140 or Early Termination (ET) and Change in PA colony-forming units (CFUs) in sputum at the end of each on-drug cycle) the MAH did not provide data in the paediatric subgroups. However based on the data in the overall population which showed no significant differences in the aforementioned tertiary endpoints (exception is the TSQM which was considered significantly different), the same is expected in the paediatric subgroups.

Within the subpopulations (6-12 and 13-17 years) no significant reduction in Log_{10} PA CFU/g was noticed. On average sputum PA in the subpopulation 6-12 years decreases in the same order of magnitude treatment difference 0.259 [mean (SE) for AZLI -3.487 (2.760); TNS -3.228 (2.701)]. In the subpopulation 13-17 years the treatment difference was -0.535 in favour of TNS [mean (SE) for

AZLI 0.053 (0.647); TNS -0.482 (0.494)].

Supplementary information provided during this procedure

The impact of AZLI treatment on hospitalization rates compared to CF patients receiving standard of care management was however further demonstrated in a case-matched controlled study utilizing data from the US CFF Registry. In this study, the durability of AZLI efficacy overall and across age groups was evaluated by comparing hospitalization data from the subset of subjects in Study CP-AI-006 originating from Study CP-AI-005 (AZLI group; N = 148; courses 1 to 6) to matched control data from the CFF Registry (control group; N = 444). The control group consisted of patients from the 2006 CFF Registry who met eligibility requirements for the CP-AI-005 trial, namely, that they had been prescribed TNS as a chronic therapy for ≥ 3 courses over the past 12 months. This group was matched against the AZLI group based on age, gender, baseline FEV_1 % predicted, baseline visit quarter (to account for seasonality), geographic region, concomitant medications (azithromycin, pancreatic enzymes), and the presence or absence of CF-related diabetes. Patients in the control group were matched in a 3:1 ratio to subjects in the AZLI group having 1-year follow-up at the time of the analysis.

Table 13 presents a comparison of hospitalizations over a 12-month period for the CP-AI-005 subset of Study CP-AI-006 (AZLI group) and the CFF Registry control group. The percent of patients hospitalized at least once was higher in the control group (54.7%) compared to the AZLI group (36.5%). These differences were more pronounced in the subgroups of subjects aged < 18 years. The mean number of hospitalization days was also lower overall for the AZLI group (6.8 days versus 11.3 days) and again, even greater differences were observed in the < 18 year old subgroups. Hospitalization rates (hospitalizations/patient-year) for subjects aged < 18 years were 0.96 for the AZLI group vs. 1.80 for the control group.

Table 13: Hospitalization Summary over 12 months (CP-AI-005 Subset of Study CP-AI-006 [AZLI Group] and CFF Registry Control Group)

	Age Group (years)				**Total**
	6 to 12	**13 to 17**	**< 18**	**≥ 18**	
CFF Registry					
	N = 24	**N = 75**	**N = 99**	**N = 345**	**N = 444**
Number of Patients Never Hospitalized n (%)	**6 (25.0)**	**25 (33.3)**	**31 (31.3)**	**170 (49.3)**	**201 (45.3)**
Number of Patients Hospitalized at Least Once n (%)	**18 (75.0)**	**50 (66.7)**	**68 (68.7)**	**175 (50.7)**	**243 (54.7)**
Number of Hospitalization Days Mean (SD)	**10.8 (10.2)**	**19.8 (29.2)**	**17.6 (26.2)**	**9.4 (17.7)**	**11.3 (20.2)**
Total Number of Hospitalizations	**29**	**131**	**160**	**341**	**501**
CP-AI-005 Subset of CP-AI-006[a]					
	N = 7	**N = 23**	**N = 30**	**N = 118**	**N = 148**
Number of Patients Never Hospitalized n (%)	**4 (57.1)**	**12 (52.2)**	**16 (53.3)**	**78 (66.1)**	**94 (63.5)**
Number of Patients	**3 (42.9)**	**11 (47.8)**	**14 (46.7)**	**40 (33.9)**	**54 (36.5)**

	Age Group (years)				Total
	6 to 12	13 to 17	< 18	≥ 18	
Hospitalized at Least Once n (%)					
Number of Hospitalization Days Mean (SD)	**7.1 (13.9)**	**6.3 (7.8)**	**6.5 (9.3)**	**6.9 (24.7)**	**6.8 (22.4)**
Total Number of Hospitalizations	**6**	**13**	**19**	**77**	**96**

Source: CFF Registry Table 4.1, A2RM #5175 Tables 1-4; EMEA Tables 124.5.1, 124.5.2.1 – 124.5.2.4 - available on request

a Pooled BID and TID groups

Clinical studies in special populations

Not applicable

Supportive study

Study EA-US-205-0111

Although Study EA-US-205-0111 was not included in the agreed AZLI Paediatric Investigation Plan, the results are used as supportive data in this Type II Variation to expand the indication to paediatric patients.

Study EA-US-205-0111 was an open-label, expanded access program for subjects ≥6 years of age with CF and chronic *PA* infection that were at high risk for disease progression.

The primary objective of this programme was to provide expanded access to AZLI 75 mg TID prior to its commercial availability to patients in the US with CF and chronic PA airway infection who had limited treatment options and were at risk for disease progression. This was an open-label programme with no formal hypothesis testing planned. Serious adverse events (SAEs) were collected and data were summarized descriptively.

Subjects with CF and chronic PA cultured from either sputum or throat swab and limited treatment options were eligible in the following cohorts:

1. Those who were waitlisted or eligible for lung transplant based on forced expiratory volume in 1 second (FEV_1) criteria, or completed participation in the open-label trial CP-AI-006; subjects who had a level of lung function impairment consistent with lung transplantation criteria, but who were ineligible for transplantation for other reasons, could enrol in this program.
2. $FEV_1 \leq 40\%$ predicted;
3. $FEV_1 \leq 50\%$ predicted

Subjects who met the inclusion/exclusion criteria could receive AZLI 75 mg TID in 56-day cycles of therapy (28 days on AZLI followed by 28 days off) until 1 of the following events occurred: voluntary withdrawal from study, the investigator requested withdrawal for subject benefit, death, new drug application (NDA) approval by the FDA, or study termination by Gilead. EA-US-205-0111 had no limit on the number of patients who could participate and the study is now complete.

This submission presents the long-term safety data for *PA*-infected patients with CF, aged 6 years and

older, treated with Cayston in Study EA-US-205-0111. The final CSR provided with this submission is in accordance with Article 46 of Regulation (EC) No 1901/2006.

This submission presents the final long-term safety data for *PA* infected patients with CF, aged 6 years and older, treated with Cayston in Study EA-US-205-0111 (Table 14).

Table 14: Overview of Study EA-US-205-0111

Study (Module 5 Reference)	Design	Geographic Location	Study Population	Treatment	Subjects Treated	Duration
EA-US-205-0111 (m5.3.5.2)	**Open-label, multicenter, Phase 3, expanded access program for subjects with CF and *PA* airway infection**	**65 sites in the US**	**Subjects ≥ 6 years of age with CF and chronic *PA* airway infection who had limited treatment options and were at risk for disease progression**	**AZLI 75 mg TID**	**Total: 603 subjects 26 subjects aged 6 to 12 years 82 subjects aged 13 to 17 years 495 subjects aged ≥ 18 years**	**Up to 19 treatment cycles of 28 days, each followed by a 28-day off-treatment period**

EA-US-205-0111 was thus a compassionate-use programme in which no efficacy data were collected. The safety results are discussed in the clinical safety section.

Discussion

Assessment of paediatric data on clinical efficacy

During the initial MAA, the indication in adults was granted based on two short term placebo controlled studies (CP-AI-005 and CP-AI-007) and an open-label long term study (CP-AI-006). During that time only data on 83 paediatric patients was available. As long term data from the pivotal study were lacking and taking into account the small numbers of paediatric patients, the indication granted referred to "short term treatment in adults only". Long term data from the pivotal study GS-US-205-0110 became available after granting the MAA. Furthermore additional safety data has become available (GS-US-205-0111, and GS-US-205-0117).

Based on the presented data on paediatric patients (aged 6-17 years), it is concluded that still only small numbers of paediatric patients were included in the clinical studies and no studies focused on paediatric patients only. Of the 681 patients enrolled in these trials, only 179 comprised unique paediatric patients. From these 179 paediatric patients only 59 were enrolled in the double blind, active comparator controlled study GS-US-205-0110.

Based on the paediatric data from all efficacy studies, a similar trend is observed as in the adult population, although results in the paediatric populations generally did not reach statistical significance. FEV_1 percentage predicted and the change in $\log_{10}$ PA CFU/g were better in the AZLI treated group compared to placebo (pooled study **CP-AI-005 and CP-AI-007**). The same trend was observed in study **CP-AI-006**, although the value of the latter study can be questioned, due to factors such as open-label design, heterogenicity of the included patients and use of co-medication.

In study **GS-US-205-0117** the $\log_{10}$ PA CFU/g sputum significantly decreased at day 28 for the

overall AZLI treated population (paediatric patients and adults) compared to placebo.

The pivotal comparative study **GS-US-205-0110** showed that patients <18 years (n=28) treated with AZLI TID showed improvement in FEV_1 % predicted both at day 28 and after 3 treatment courses compared to TNS treated patients (treatment difference -6.26, -2.14, respectively). The improvement in FEV_1 followed the same trend as in adults.

For time to Need for IV Anti-PA Antibiotics for Respiratory Event and Time to first respiratory hospitalisation, no difference in the events between the AZLI and TNS treated paediatric patients was observed.

The MAH further provided supplementary data from 30 paediatric subjects as a subset from another study that compared hospitalization rates with an external data source to refute the findings from study GS-US-205-0110. The presented open label study CP-IA-006 was a comparison of BID and TID during different periods of follow up, which might give an indication of the eventual translation of FEV1 changes into the reduction of need of additional treatment/hospitalisation, but the study was not designed for these purposes. Furthermore, the comparison with data from CF patients included in other (non-study) settings with different treatment modalities might also be illustrative, but cannot be used to support or deny any claim of reduced rates of hospitalization in this age group compared to standard of care (i.e. TNS).

Conclusions on clinical efficacy

In general, the interpretation of the results from all subgroup analyses should be done cautiously as only small numbers of paediatric patients were included in the different trials and inclusion criteria and co-medication were different.

2.4.3. Clinical safety aspects

Adverse events in paediatric patients

Short term studies

Phase 2/3 Placebo-Controlled Studies (CP-AI-003, CP-AI-005, and CP-AI-007)

For the integrated Phase 2/3 placebo-controlled studies (CP-AI-003, CP-AI-005, and CP-AI-007), the incidence of many respiratory AEs and ADRs was higher among adult subjects (≥ 18 years of age), consistent with the general observation of increased disease severity in adult patients with CF (Table 15).

Table 15: Respiratory AEs and/or ADRs[a] by Age Group: Integrated Studies CP-AI-003, CP-AI-007, and CP-AI-005

Preferred Term	Children (6-12 years)	Adolescents (13-17 years)	Adults (≥ 18 years)

	Placebo (N = 5) n (%)	AZLI (N = 20) n (%)	Placebo (N = 29) n (%)	AZLI (N = 56) n (%)	Placebo (N = 157) n (%)	AZLI (N = 213) n (%)
Chest discomfort	*0*	*0*	*1 (3.4)*	*4 (7.1)*	*9 (5.7)*	*20 (9.4)*
Cough	*2 (40.0)*	*12 (60.0)*	*17 (58.6)*	*33 (58.9)*	*75 (47.8)*	*104 (48.8)*
Dyspnoea	0	0	2 (6.9)	5 (8.9)	17 (10.8)	21 (9.9)
Dyspnoea exacerbated	0	1 (5.0)	0	1 (1.8)	14 (8.9)	7 (3.3)
Dyspnoea exertional	0	1 (5.0)	2 (6.9)	1 (1.8)	6 (3.8)	10 (4.7)
Haemoptysis	0	1 (5.0)	1 (3.4)	3 (5.4)	21 (13.4)	19 (8.9)
Nasal congestion	0	5 (25.0)	6 (20.7)	9 (16.1)	17 (10.8)	30 (14.1)
Non-cardiac chest pain	0	1 (5.0)	0	0	7 (4.5)	6 (2.8)
Pharyngolaryngeal pain	0	2 (10.0)	3 (10.3)	10 (17.9)	17 (10.8)	23 (10.8)
Productive cough	0	5 (25.0)	11 (37.9)	14 (25.0)	50 (31.8)	58 (27.2)
Respiratory tract congestion	0	0	0	3 (5.4)	19 (12.1)	23 (10.8)
Rhinorrhoea	2 (40.0)	5 (25.0)	3 (10.3)	6 (10.7)	8 (5.1)	13 (6.1)
Sinus congestion	0	0	1 (3.4)	4 (7.1)	10 (6.4)	14 (6.6)
Wheezing	0	2 (10.0)	1 (3.4)	3 (5.4)	17 (10.8)	33 (15.5)
Pyrexia	0	5 (25.0)	0	9 (16.1)	11 (7.0)	18 (8.5)
Forced expiratory volume decreased[b]	*0*	*2 (10.0)*	*1 (3.4)*	*0*	*5 (3.2)*	*6 (2.8)*
Pulmonary function test decreased	1 (20.0)	1 (5.0)	3 (10.3)	2 (3.6)	11 (7.0)	14 (6.6)
Rash	0	0	0	1 (1.8)	3 (1.9)	4 (1.9)

a Those preferred terms considered ADRs are presented in italicized text. ADRs were those events reported in more than 5% of subjects treated with AZLI TID in the placebo-controlled Phase 3 trials.

b Bronchospasm in clinical trials of AZLI was defined as a reduction of 15% or more in FEV_1 immediately following administration of study medication after pretreatment with a bronchodilator.

Some AEs were observed in a higher overall proportion of paediatric patients treated with AZLI. Of particular interest were the AEs that were previously identified as possible ADRs to AZLI. Among these ADRs, higher percentages were observed in children (compared to adults) for certain events, namely cough (59.2% of paediatric patients vs. 48.8% of adults), pyrexia (18.4% vs. 8.5%), pharyngolaryngeal pain (15.8% vs. 10.8%), nasal congestion (18.4% vs. 14.1%), and rhinorrhoea (14.5% vs. 6.1%).

Fever is a common symptom among patients with CF, as evidenced by the TOBI registration trials in which fever was reported in 44% of placebo-treated subjects (TOBI Package Insert). In studies with AZLI, pyrexia occurred in similar proportions of adult subjects in the pooled AZLI (9%) and placebo (7%) groups. However, among AZLI-treated subjects < 18 years of age, the incidence of pyrexia was 16% for adolescents (13 to 17 years of age) and 25% for children (6 to 12 years of age), but no AEs of pyrexia were reported for subjects treated with placebo < 18 years of age. One interpretation of these observations is that AEs of pyrexia may be a response to endotoxin release from bacterial killing and that children are more likely to exhibit a febrile response than adults, who may have developed endotoxin tolerance (West, Michael A, Heagy, Wyrta Endotoxin tolerance: A review; Critical Care Medicine, Volume 30, Issue 1 [January 2002], SS64-S73).

Comment:

Based on table presented above no extra AEs or ADRs are observed in study CP-AI-003, CP-AI-005 and CP-AI-007. "Haemoptysis" frequency within the paediatric and adult population appears to be similar compared to the corresponding placebo group (table 15). Although "pyrexia" shows similar frequencies in the adult population, in paediatric patients pyrexia shows higher frequencies (6-12 years: 25% (n=5) and 13-17 years: 16.1%, n=9).

Study GS-US-205-0117

This study enrolled subjects with CF and chronic PA infection at high risk for disease progression, which included those with moderate to severe lung function impairment and limited treatment options and those who had completed participation in Study CP AI 006.

The most commonly reported treatment-emergent AE in this study was cough, which occurred in 35 (46%) AZLI-treated subjects and 31 (38%) placebo-treated subjects. Productive cough was the next most common AE (18 [23.7%] AZLI-treated subjects and 3 [16.0%] placebo-treated subjects), followed by nasal congestion (13 [17.1%] AZLI-treated subjects and 15 [18.5%] placebo-treated subjects). A greater percentage of AZLI-treated subjects reported treatment-related AEs (13 [17.1%]) compared to placebo-treated subjects (7 [8.6%]) (p = 0.151). Related cough was reported by 7 (9.2%) AZLI-treated subjects and 4 (4.9%) placebo-treated subjects. An equal number of subjects in each treatment group reported related productive cough, 3 (3.9%) AZLI-treated subjects and 3 (3.7%) placebo-treated subjects. Pyrexia was reported for 8 (9.9%) placebo-treated subjects and 6 (7.9%) AZLI-treated subjects. All incidences of pyrexia were considered unlikely to be related to study drug. None of the differences in AEs were statistically significant between the AZLI and placebo groups.

Table 16: Treatment-Emergent AEs Reported in At Least 10% of Subjects by Age Group, Study GS-US-205-0117

	Children (6-12 years)		**Adolescents (13-17 years)**		**Adults (≥ 18 years)**	
Preferred Term	**Placebo (N = 18) n (%)**	**AZLI (N = 14) n (%)**	**Placebo (N = 29) n (%)**	**AZLI (N = 28) n (%)**	**Placebo (N = 34) n (%)**	**AZLI (N = 34) n (%)**
Cough	11 (61.1)	6 (42.9)	11 (37.9)	16 (57.1)	9 (26.5)	13 (38.2)
Nasal Congestion	6 (33.3)	0	5 (17.2)	5 (17.9)	4 (11.8)	8 (23.5)
Headache	3 (16.7)	3 (21.4)	2 (6.9)	7 (25.0)	5 (14.7)	4 (11.8)
Oropharyngeal Pain	2 (11.1)	3 (21.4)	6 (20.7)	4 (14.3)	3 (8.8)	5 (14.7)
Productive Cough	4 (22.2)	2 (14.3)	3 (10.3)	6 (21.4)	6 (17.6)	10 (29.4)
Pulmonary Function Test Decreased	3 (16.7)	2 (14.3)	5 (17.2)	4 (14.3)	1 (2.9)	1 (2.9)
Fatigue	3 (16.7)	1 (7.1)	3 (10.3)	2 (7.1)	4 (11.8)	3 (8.8)
Rhinorrhoea	3 (16.7)	1 (7.1)	3 (10.3)	2 (7.1)	6 (17.6)	5 (14.7)
Nausea	2 (11.1)	0	1 (3.4)	1 (3.6)	3 (8.8)	1 (2.9)
Pyrexia	2 (11.1)	0	3 (10.3)	3 (10.7)	3 (8.8)	3 (8.8)

Preferred Term	Children (6-12 years)		Adolescents (13-17 years)		Adults (≥ 18 years)	
	Placebo (N = 18) n (%)	AZLI (N = 14) n (%)	Placebo (N = 29) n (%)	AZLI (N = 28) n (%)	Placebo (N = 34) n (%)	AZLI (N = 34) n (%)
Respiratory Tract Congestion	0	1 (7.1)	3 (10.3)	5 (17.9)	3 (8.8)	5 (14.7)
Decreased Appetite	0	0	0	4 (14.3)	0	2 (5.9)
Dyspnoea	0	1 (7.1)	1 (3.4)	3 (10.7)	3 (8.8)	3 (8.8)
Wheezing	0	1 (7.1)	2 (6.9)	3 (10.7)	3 (8.8)	1 (2.9)
Diarrhoea	1 (5.6)	0	6 (20.7)	0	2 (5.9)	3 (8.8)
Postnasal Drip	1 (5.6)	0	3 (10.3)	2 (7.1)	3 (8.8)	1 (2.9)
Rales	1 (5.6)	1 (7.1)	3 (10.3)	2 (7.1)	1 (2.9)	4 (11.8)
Abdominal Pain	1 (5.6)	0	6 (20.7)	1 (3.6)	3 (8.8)	0
Chest Discomfort	0	0	1 (3.4)	1 (3.6)	1 (2.9)	5 (14.7)
Sinus Headache	0	0	0	0	3 (8.8)	5 (14.7)
Throat Irritation	0	0	0	1 (3.6)	4 (11.8)	0

The AEs of cough and pulmonary function test decreased were observed at a higher frequency in paediatric patients compared to adults; however, these events occurred at a similar frequency between AZLI- and placebo-treated paediatric patients. Pyrexia occurred at similar rates between placebo- and AZLI-treated subjects and no age-related differences were observed.

Comment:

The reported AEs from study GS-US-205-0117 do not raise any concern as AEs reported for AZLI are comparable to the frequency reported in the placebo group. AZLI related AEs are comparable between adults and the paediatric patients. Pyrexia was observed in both the paediatric and adult population in equal frequencies.

Interestingly enough, although only small numbers are reported, both in placebo and in AZLI, similar frequencies of "Pulmonary Function Test Decreased" are observed.

Haemoptysis is not listed in table 16. As haemoptysis was observed in the other studies, the MAH was requested to submit the data on haemoptysis in children, if available.

Supplementary information provided during this procedure

A total of 3 subjects reported haemoptysis during Study GS-US-205-0117, only 1 of whom was treated with AZLI (Table 17). The remaining two reports of haemoptysis occurred in placebo-treated subjects and are not discussed further.

Table 17: Treatment-Emergent Rates of Haemoptysis by Age Group in Study GS-US-205-0117

<18 Years		≥18 Years	
Placebo n = 47	**AZLI n = 42**	**Placebo n = 34**	**AZLI n = 34**
1 (2.1%)	**1 (2.4%)**	**1 (2.9%)**	**0 (0.0%)**

The AZLI-treated subject was a 17-year-old female with a medical history that included hemoptysis prior to study enrollment, bronchiectasis, *Staphylococcus aureus*, and multiple hospitalizations for CF exacerbations. The subject experienced 2 episodes of haemoptysis that were non-serious and mild. One episode occurred during the on-treatment cycle of AZLI therapy; no action was taken with AZLI and the subject recovered while AZLI therapy continued unchanged. The other episode occurred during the off-treatment cycle. Neither episode of haemoptysis was associated with bronchospasm. The investigator assessed both episodes of haemoptysis as not related to AZLI.

Long term Studies

Study CP-AI-006

Although not a controlled study, the overall AE profile observed in Study CP-AI-006 was generally similar among adult and paediatric patients. Of the 274 subjects participating in Study CP-AI-006, **55** (20%) were paediatric patients (age < 18 years) and **219** were adults (age ≥ 18 years) (80%).

For the study as a whole, 213 of 219 (97.3%) adult subjects (≥ 18 years of age) reported at least one AE versus 55 of 55 (100.0%) paediatric patients (<18 years of age). Of the AEs reported with an incidence rate ≥ 10% in either age group, the following AEs occurred in a higher percentage (≥ 5% difference) of subjects <18 years of age than adult subjects: cough, pharyngolaryngeal pain, pyrexia, headache, rhinorrhea, crackles lung, pulmonary function test decreased, vomiting, non-cardiac chest pain, weight decreased, abdominal pain, abdominal pain upper, constipation, epistaxis, blood glucose increased, and rhonchi. In contrast the following AEs occurred in a higher percentage (≥ 5% difference) of adult subjects than subjects < 18 years of age: respiratory tract congestion, wheezing, chest discomfort, sinus congestion, diarrhea, sinus headache, back pain, dyspnea exacerbated, chills, and myalgia.

Comments:

Previously (PSUR1- assessment report dated May 2010) the CHMP concluded: Overall, safety data from the completed Study CP-AI-006 in which patients were treated with up to 9 courses of Cayston over 18 months did not reveal new safety concerns. No drug-related systemic SAEs occurred, and there were no meaningful haematological or chemistry findings.

Haemoptysis was reported in both adults (≥18 years) and children (<18 years) 73/219 (33.3%) versus 19/55 (34.5%) respectively.

It is noticed that in paediatric patients the AE pulmonary function test decreased (40%) which was

remarkably higher than in adults (18.3%). Furthermore it was also noticed that the AEs appeared more frequently in AZLI compared to placebo: crackles lung (34.5% vs 21.0%), vomiting (38.2% vs 18.3%), pyrexia (54.5% vs 43.3%). The MAH should state these AEs in the SmPC.

Study GS-US-205-0110, Randomised Phase

Treatment-emergent AEs are presented by SOC and age in Table 18. All subjects under 18 years of age reported at least one AE compared to 94.4% and 96.0% of AZLI- and TNS-treated subjects ≥ 18 years of age, respectively. The most common treatment-emergent AEs in all age groups were respiratory, most frequently cough and productive cough. Higher percentages of adolescents (< 18 years of age) reported pyrexia in the AZLI- and TNS-treated groups (46.4% and 41.9%, respectively) than adults (27.8% and 26.7%, respectively). Also, in adolescents aged 13 to 17 years, a higher percentage of AZLI-treated subjects reported haemoptysis than TNS-treated subjects (21.4% [5 subjects] vs. 3.2% [1 subject], respectively). One of the haemoptysis events resulted in hospitalization for an AZLI-treated subject (0602-621); the event was judged by the investigator to be severe but unrelated to study drug.

Table 18: Treatment-Emergent AEs Reported by ≥ 5% of the Subjects in Either Treatment Group by Age (Safety Population), Study GS-US-205-0110, Randomised Phase

System Organ Class Event (Preferred Term)	6 – 12 years		13 – 17 years		< 18 years		≥ 18 years	
	AZLI (n = 8)	TNS (n = 5)	AZLI (n = 20)	TNS (n = 26)	AZLI (n = 28)	TNS (n = 31)	AZLI (n = 108)	TNS (n = 101)
Cough	8 (100.0)	5 (100.0)	16 (80.0)	23 (88.5)	24 (85.7)	28 (90.3)	72 (66.7)	76 (75.2)
Haemoptysis	1 (12.5)	0	5 (25.0)	1 (3.8)	6 (21.4)	1 (3.2)	25 (23.1)	20 (19.8)
throat Irritation	0	0	1 (5.0)	0	1 (3.6)	0	5 (4.6)	1 (1.0)
Pyrexia	4 (50.0)	2 (40.0)	9 (45.0)	11 (42.3)	13 (46.4)	13 (41.9)	30 (27.8)	27 (26.7)
Exercise Tolerance Decreased	2 (25.0)	0	5 (25.0)	6 (23.1)	7 (25.0)	6 (19.4)	18 (16.7)	21 (20.8)
Gastrointestinal Disorders	4 (50.0)	2 (40.0)	4 (20.0)	9 (34.6)	8 (28.6)	11 (35.5)	38 (35.2)	34 (33.7)
Vomiting	1 (12.5)	2 (40.0)	1 (5.0)	5 (19.2)	2 (7.1)	7 (22.6)	12 (11.1)	7 (6.9)
Abdominal Pain	2 (25.0)	0	3 (15.0)	0	5 (17.9)	0	13 912.0)	8 (7.9)
Pulmonary Function Test Decreased	1 (12.5)	0	4 (20.0)	3 (11.5)	5 (17.9)	3 (9.7)	6 (5.6)	14 (13.9)
Forced Expiratory Volume Decreased	3 (37.5)	1 (20.0)	2 (10.0)	0	5 (17.9)	1 (3.2)	4 (3.7)	4 (4.0)
Musculoskeletal and Connective Tissue Disorders	0	0	3 (15.0)	3 (11.5)	3 (10.7)	3 (9.7)	27 (25.0)	20 (19.8)
Infections and Infestations	3 (37.5)	2 (40.0)	2 (10.0)	5 (19.2)	5 (17.9)	7 (22.6)	22 (20.4)	18 (17.8)

Rhinitis	1 (12.5)	0	0	0	1 (3.6)	0	3 (2.8)	7 (6.9)
Onychomycosis	1 (12.5)	0	0	0	1 (3.6)	0	1 (0.9)	0
Nasopharyngitis	0	1 (20.0)	0	0	0	1 (3.2)	0	0
Upper Respiratory Tract Infection	0	1 (20.0)	0	0	0	1 (3.2)	0	0
Varicella	1 (12.5)	0	0	0	1 (3.6)	0	0	0
Metabolism and Nutrition Disorders	4 (50.0)	0	4 (20.0)	6 (23.1)	8 (28.6)	6 (19.4)	15 (13.9)	22 (21.8)
Skin and Subcutaneous Tissue Disorders	2 (25.0)	0	5 (25.0)	0	7 (25.0)	0	14 (13.0)	12 (11.9)
Psychiatric Disorders	0	0	0	0	0	0	9 (8.3)	7 (6.9)
Injury, Poisoning, and Procedural Complications	0	0	3 (15.0)	0	3 (10.7)	1 (3.2)	5 (4.6)	3 (3.0)
Cardiac Disorders	0	0	0	2 (7.7)	0	2 (6.5)	6 (5.6)	3 (3.0)
Ear and Labyrinth Disorders	0	0	1 (5.0)	2 (7.7)	1 (3.6)	2 (6.5)	6 (5.6)	1 (1.0)
Vascular Disorders	0	0	1 (5.0)	2 (7.7)	1 (3.6)	2 (6.5)	1 (0.9)	4 (4.0)
Blood and Lymphatic System Disorders	0	0	1 (5.0)	0	1 (3.6)	0	0	0

Multiple occurrences per subject are counted once per SOC and PT.

Comment:

The reported AEs in study GS-US-205-0110 are in the same order of frequency between paediatric patients and adults. Cough and reproductive cough were most commonly reported. Pyrexia and haemoptysis were reported more frequently in paediatric patients treated with AZLI compared to both the TNS treated patients and the patients >18 years.

Pyrexia was reported more frequently in paediatric patients (<18 years of age) both in the AZLI- and TNS-treated groups (46.4% and 41.9%, respectively compared to the adults (27.8% and 26.7%, respectively).

In AZLI treated adolescents aged 13 to 17 years **haemoptysis** was reported more frequently than TNS-treated subjects (21.4% [5 subjects] vs. 3.2% [1 subject], respectively). Most likely, AZLI will not directly damage the bronchial wall resulting in haemorrhage and subsequent haemoptysis. Whether haemoptysis results from the induced bronchospasms due to the rapid administration of AZLI remains to be determined. Support for this hypothesis may be derived from decreases in lung function in AZLI-treated paediatric patients compared to TNS. This identified safety risk is to be addressed in the RMP and to be mentioned in the SmPC.

Study GS-US-205-0110, Extension Phase

In the extension phase of Study GS-205-0110, all subjects under 13 years of age reported at least 1 AE compared to 100% and 93.3% of AZLI/AZLI- and TNS/AZLI-treated subjects ≥ 13 to 18 years of age, respectively. The most common treatment-emergent AEs in both subjects under 13 years of age and in subjects ≥ 13 to 18 years of age were cough (57.1% and 73.9%), productive cough (42.9% and 47.8%), and pyrexia (42.9% and 30.4%, respectively).

***Comments**:*

Overall the patients <18 years experienced less frequently AEs. The most common treatment-emergent AEs in both subjects under 13 years of age and in subjects > 13 to 18 years of age were cough (57.1% and 73.9%), productive cough (42.9% and 47.8%), and pyrexia (42.9% and 30.4%, respectively).

Summary of Adverse Event Data

The safety results from Study GS-US-205-0110 are consistent with results from the previously reported Phase 2/3 clinical studies of AZLI and support the use of Cayston in patients ≥ 6 years of age over repeated courses of treatment. In the randomised phase of Study GS-US-205-0110, AZLI was well-tolerated over 3 treatment courses with an AE profile consistent with the previously established clinical trial experience for AZLI. Respiratory AEs were the most frequently reported treatment-emergent AEs. A significantly higher percentage of subjects in the AZLI group reported drug-related AEs in comparison to subjects in the TNS group. In this unblinded study, investigators familiar with TNS may have attributed more AEs to a less familiar antibiotic (AZLI). In the extension phase, a similar percentage of subjects reported at least 1 AE in each treatment group and phase (range: 92.6% to 97.0%). The percentages of subjects reporting respiratory AEs overall (range: 86.8% to 93.9%) and cough (range: 69.1% to 78.8%) were similar, regardless of randomised treatment group and phase. In both cases the lowest percentage of subjects reporting these did so during the extension phase after treatment with AZLI during the randomized phase. Similarly, productive cough and hemoptysis were reported by the lowest percentage of subjects (38.2% and 11.8%, respectively) during the extension phase after treatment with AZLI in the randomized phase. The percentage of subjects reporting pyrexia was highest (40%) in the extension phase among subjects who received TNS during the randomized phase. Percentages for pyrexia for the 3 remaining treatment and phase subgroups ranged from 29.4% to 31.6%. Treatment-emergent AE rates adjusted for duration on study were lower during the extension phase regardless of randomized treatment with the exception of pyrexia, diarrhea, weight decreased, and arthralgia, although the rate differences for these exceptions were less than 3%.

Based on the review of the safety profile of AZLI in paediatric patients, AZLI is well-tolerated in paediatric patients aged 6 years and older and no new safety concerns have arisen following a review of the safety data from paediatric patients. In the Phase 2/3 controlled clinical registration studies of AZLI, the incidence of many respiratory AEs was higher among adult subjects (≥ 18 years of age) than paediatric patients (< 18 years of age); however, pyrexia was observed at a higher incidence rate in paediatric patients (18%) compared to adults (8%). The higher incidence of respiratory AEs in adults is consistent with the general observation of increased disease severity in adult patients with CF. In the randomized phase of Study GS-US-205-0110, the most common treatment-emergent AEs in paediatric patients were respiratory, most frequently cough and productive cough; consistent with the findings of previously completed AZLI studies (Studies CP-AI-003, CP-AI-005, CP-AI-006, CP-AI-007, and GS-US-205-0117).

Comment:

In general the observed AEs in paediatric patients are comparable to the AEs observed in adults.

Haemoptysis is of concern especially in children, an increase in frequency has been observed in the long term study GS-US-205-0110. Although the MAH explained in the SO2 that haemoptysis is not an ADR but related to bronchospasm, the CHMP is of the opinion that haemoptysis must be included in the SmPC and RMP as an identified risk.

Besides this concern on increased occurrence of haemoptysis in AZLI-treated paediatric patients, the CHMP agrees with the conclusion of the MAH that based on the review of the safety profile of AZLI in paediatric patients, AZLI is generally well-tolerated in paediatric patients aged 6 years and older and no new safety concerns have arisen following a review of the safety data from paediatric patients.

Serious adverse events and deaths

Short term studies

Phase 2/3 Placebo-Controlled Studies (CP-AI-003, CP-AI-005, and CP-AI-007)

Most SAEs that occurred during the Phase 2/3 placebo-controlled studies were attributable to pulmonary exacerbations. Overall a higher incidence of SAEs in paediatric patients was observed in the Phase 2/3 placebo-controlled studies, with the highest incidence occurring in children aged 6 to 12 years. Serious adverse events were reported for 16% of children aged 6 to 12 years, 8% of adolescents, and 7% of adults. Although the number of subjects aged 12 years and younger is small, and must be interpreted with caution, the higher incidence of SAEs may be at least partially attributable to the number of hospitalizations for exacerbations that occur as children are less likely to be treated as outpatients when they require intravenous (IV) antibiotics. No particular patterns of specific SAEs were noted.

Hospitalizations within the clinical trial setting can be considered to reflect both the safety and efficacy of the study drug. As anticipated for a population of patients with CF, hospitalizations for symptoms of CF pulmonary exacerbation accounted for the majority of SAEs in the AZLI clinical trials. For these analyses, hospitalization was defined as the formal admittance of a subject into a hospital for any medical reason for more than 1 calendar day. Table 19 summarizes hospitalizations by age group for the Phase 3 placebo-controlled registration studies (CP-AI-007 and CP-AI-005).

Table 19: Hospitalizations by Age Group: Integrated Studies CP-AI-007 and CP-AI-005

	Children (6-12 years)	**Adolescents (13-17 years)**	**Adults (≥ 18 years)**			
	Placebo (N = 5)	**AZLI (N = 20)**	**Placebo (N = 23)**	**AZLI (N = 35)**	**Placebo (N = 132)**	**AZLI (N = 160)**
Number (%) of subjects hospitalized at least once after first dose	0	4 (20.0)	2 (8.7)	4 (11.4)	13 (9.8)	10 (6.3)
p-value[a]	0.5494	1.0000	0.2812			
Mean (SD) days hospitalized[b]	0.00 (0.00)	2.10 (5.13)	0.65 (2.55)	0.54 (1.65)	1.08 (3.55)	0.68 (3.48)
Cause of hospitalization, n (%)[c]						
Lower respiratory	0	2 (10.0)	2 (8.7)	2 (5.7)	10 (7.6)	10 (6.3)
Upper respiratory	0	0	0	0	0	0
Gastrointestinal	0	1 (5.0)	0	0	1 (0.8)	1 (0.6)
Other	0	1 (5.0)	1 (4.3)	2 (5.7)	2 (1.5)	1 (0.6)

a Based on 2x2 Fisher's Exact test for treatment group effect between placebo and AZLI treatment groups.

b Denominator includes all subjects.

c Includes all hospitalizations over the course of the study.

Subjects are counted once per cause but may be counted in more than one cause.

Higher proportions of AZLI-treated children (aged 6 to 12 years; n = 20) and adolescents (aged 13 to 17 years; n = 35) were hospitalized compared with adults (20% children vs. 11% adolescents vs. 6% adults). However, no statistically significant differences were observed in any age subgroup for comparison of pooled AZLI versus pooled placebo groups in the number of subjects hospitalized, and the results must be interpreted with caution due to the small numbers of paediatric patients studied in these placebo-controlled AZLI trials. The mean number of days hospitalized was 2.1 days for children, 0.5 days for adolescents, and 0.7 days for adults.

Comments:

The MAH concluded that the overall higher incidence of SAEs in paediatric patients was observed in the Phase 2/3 placebo-controlled studies, with the highest incidence occurring in children aged 6 to 12 years. Serious adverse events were reported for 16% of children aged 6 to 12 years, 8% of adolescents, and 7% of adults. These events were reported to be related to pulmonary exercabations (cough, crackles lung, dyspnoea, productive cough). The SAEs were reported in both adults and paediatric patients in comparable frequencies.

Higher proportions of AZLI-treated children (aged 6 to 12 years; n = 20) and adolescents (aged 13 to 17 years; n = 35) were hospitalized compared with adults (20% children vs. 11% adolescents vs. 6% adults). However, no statistically significant differences were observed in any age subgroup for comparison of pooled AZLI versus pooled placebo groups in the number of subjects hospitalized. This may be attributed to the small number of subjects.

Study GS-US-205-0117

Overall, 12 subjects experienced a total of 20 treatment-emergent SAEs. Serious adverse events were associated with hospitalizations in all cases. Twelve subjects experienced 14 hospitalizations in total. At the time of the SAEs, no subject was 6 to 12 years of age, 7 subjects were 13 to 17 years of age, and 5 subjects were ≥ 18 years of age. In the AZLI group, 9 (11.8%) subjects reported SAEs compared with 3 (3.7%) subjects in the placebo group (p = 0.073). The most frequently reported SAEs occurred in the respiratory, thoracic and mediastinal disorders SOC, with 6 (7.9%) subjects in the AZLI group reporting SAEs in this SOC compared with 2 (2.5%) subjects in the placebo group, with the most common SAE overall being cough. Three (3.9%) subjects in the AZLI group reported an SAE of cough compared with 1 (1.2%) subject in the placebo group. None of the SAEs were considered by the investigators to be related to study drug.

Long term studies

Study CP-AI-006

A higher incidence of SAEs in paediatric patients was also noted in Study CP-AI-006 as a whole; however, the overall AE profile was otherwise generally similar among adult and paediatric patients. Overall, SAEs were reported for 56% of children aged 6 to 12 years, 51% of adolescents, and 38% of adults. Most SAEs were attributable to hospitalization for symptoms of pulmonary exacerbation. Of the SAEs occurring in ≥ 3% of subjects in any age subgroup, most events were reported at a higher incidence in paediatric patients. Within the paediatric subgroup, comparisons of the overall subgroups of children (aged 6 to 12 years; n = 18) and adolescents (aged 13 to 17 years; n = 37) generally showed a higher incidence of some SAEs among children, but these observations must be interpreted with caution because the number of subjects in each subgroup is small.

Of the subjects <18 years of age, 65.5% were hospitalized at least once compared with 45.7% of subjects ≥18 years of age. The overall hospitalization rates per subject year were 1.299 and 0.830 for

subjects <18 years of age and subjects ≥18 years of age, respectively. In both age groups, the cause of hospitalization was primarily lower respiratory tract symptoms with hospitalization rates for respiratory events at 1.219 and 0.775 for subjects <18 years of age and subjects ≥18 years of age, respectively. As stated above, the higher incidence of hospitalizations in paediatric patients in the AZLI trials may reflect the subjects' relatively severe underlying CF disease, the prevailing standard of care in which paediatric patients are more likely to be hospitalized compared to adults, and parental concerns.

Based on the long-term data from Study CP-AI-006, the repeated use of AZLI over nine 28-day intermittent treatment courses (18 months) is well-tolerated for adult and paediatric patients aged 6 years and older.

Comment:

The higher incidence of hospitalisation in paediatric patients can be attributed to the severity of CF in children and the prevailing standard of care. Data on admission due to haemoptysis should be provided.

With respect to the safety no additional concerns are raised based on study CP-AI-006.

Study GS-US-205-0110, Randomised Phase

In subjects < 18 years, a greater percentage of subjects reported SAEs in the AZLI treated group (12 [42.9%]), than in the TNS treated group (8 [25.8%]). In subjects 13 to 17 years, a greater percentage of subjects reported SAEs in the AZLI treated group (10 [50.0%]), than in the TNS treated group (8 [30.8%]). In subjects 6 to 12 years, a greater percentage of subjects reported SAEs in the AZLI treated group (2 [25.0%]), than in the TNS treated group (0). Among subjects ≥ 18 years, a lower percentage of subjects reported treatment-emergent SAEs in the AZLI treated group (30 [27.8%]), than in the TNS treated group (36 [35.6%]).

Among subjects < 18 years of age, cough was reported by 8 subjects (28.6%) treated with AZLI and 5 subjects (16.1%) treated with TNS. Cough was reported among subjects ≥ 18 years of age by a similar percentage of subjects treated with AZLI (19 [17.6%]) and TNS (21 [20.8%]).

Productive cough was reported among subjects ≥ 18 years of age by a lower percentage of subjects treated with AZLI (12 [11.1%]) compared to subjects treated with TNS (18 [17.8%]). Similar percentages of subjects in each treatment group reported productive cough among subjects < 18 years of age (AZLI: 4 [14.3%], TNS: 5 [16.1%]), subjects 13 to 17 years of age (AZLI: 4 [20.0%], TNS: 5 [19.2%]), and subjects 6 to 12 years of age
(AZLI: 0, TNS: 0).

Dyspnea was reported among subjects ≥ 18 years of age by a lower percentage of subjects treated with AZLI (8 [7.4%]) compared to subjects treated with TNS (12 [11.9%]). Similar percentages of subjects in each treatment group reported dyspnea among subjects < 18 years of age (AZLI: 2 [7.1%], TNS: 3 [9.7%]), subjects 13 to 17 years of age (AZLI: 2 [10.0%], TNS: 3 [11.5%] and subjects 6 to 12 years of age (AZLI: 0, TNS: 0).

Among subjects ≥ 18 years of age, pyrexia was reported by a similar percentage of subjects treated with AZLI (8 [7.4%]) and TNS (8 [7.9%]). Among subjects < 18 years of age, pyrexia was reported by a greater percentage of subjects treated with AZLI (3 [10.7%]) than subjects treated with TNS (0). Of the 3 subjects < 18 years of age who reported pyrexia, all 3 were 13 to 17 years of age.

Comment:

Pyrexia was reported by a similar percentage of subjects treated with AZLI (8 [7.4%]) and TNS (8 [7.9%]). Among subjects <18 years of age, pyrexia was reported by a greater percentage of subjects treated with AZLI (3 [10.7%]) than subjects treated with TNS (0%).

Study GS-US-205-0110, Extension Phase

In the extension phase of Study GS-205-0110, 1 AZLI/AZLI-treated subject (25.0%) and 1 TNS/AZLI-treated subject (33.3%) under 13 years of age reported at least 1 SAE compared to 1 AZLI/AZLI-treated (12.5%) subject and 4 TNS/AZLI-treated subjects (26.7%) ≥ 13 to 18 years of age, respectively. The most common treatment-emergent SAEs in subjects under 18 years of age were productive cough (1 TNS/AZLI-treated subject under 13 years of age; 4 TNS/AZLI-treated subjects ≥ 13 to 18 years of age) and cough (1 TNS/AZLI-treated subject under 13 years of age; 3 TNS/AZLI-treated subjects ≥ 13 to 18 years of age), and decreased appetite (1 TNS/AZLI-treated subject under 13 years of age; 1 AZLI/AZLI- and 1 TNS/AZLI-treated subject ≥ 13 to 18 years of age).

Study EA-US-205-0111

A total of 626 subjects were screened at 65 study sites in the US. Of the 603 treated subjects, 344 subjects (57.0%) prematurely discontinued study treatment, primarily due to subject request. Subjects ranged in age from 6 to 66 years, with a mean (SD) age of 28.8 (11.68) years. Twenty-six subjects (4.3%) were 6 to 12 years of age and 82 subjects (13.6%) were 13 to 17 years of age. Three hundred fourteen subjects (52.1%) were female. Five hundred seventy-six subjects (95.5%) were white. The mean (SD) FEV1 % predicted at baseline was 40.37 (16.13); 494 subjects (82.4%) had baseline FEV1 ≤ 50% predicted, including 338 subjects (56.4%) with baseline FEV1 ≤ 40% predicted.

In Study EA-US-205-0111, 108 paediatric patients received at least 1 dose of AZLI, 26 subjects aged 6 to 12 years and 82 subjects aged 13 to 17 years. The safety data from this study are consistent with results from the previous Phase 2/3 studies and support the use of AZLI in CF subjects ≥ 6 years of age over repeated courses of treatment.

Discontinuations due to SAEs

A total of 37 subjects (6.1%) discontinued study drug as a result of SAEs. Lung disorder was the most frequent SAE leading to discontinuation (29 subjects [4.8%]).

No subjects in the 6 to 12 year age group discontinued due to SAEs. In the 13 to 17 year age group and ≥18 year age group, 10 subjects (12.2%) and 27 subjects (5.5%) discontinued due to SAEs, respectively, predominantly due to lung disorder (9 subjects [11.0%] and 20 subjects [4.0%], respectively).

The 3 subjects (0.5%) who experienced 1 drug-related SAE each during the study also withdrew from the study. Reasons for withdrawal associated with these SAEs (spontaneous abortion, lung disorder, and haemoptysis) were recorded as pregnancy, death, and haemoptysis, respectively.

Table 20: EA-US-205-0111: Treatment-Emergent SAEs by Severity Reported for ≥ 0.5% of All subjects by Age Group (6 to 12 years and 13 to 17 years) (Safety Analysis Set)

System Organ Class Event (Preferred Term)	6 to 12 years (N = 26)		13 to 17 years (N = 82)		< 18 years (N = 108)		≥ 18 years (N = 495)	
	Number of Subjects[a] n (%)	Duration-Adjusted Event Rate[b]	Number of Subjects[a] n (%)	Duration-Adjusted Event Rate[b]	Number of Subjects[a] n (%)	Duration-Adjusted Event Rate[b]	Number of Subjects[a] n (%)	Duration-Adjusted Event Rate[b]
Any Treatment-Emergent SAE	20 (76.9)	0.134	66 (80.5)	0.191	86 (79.6)	0.174	267 (53.9)	0.099
Cardiac Disorders	0	0	0	0	0	0	4 (0.8)	<0.001
Cardio-Respiratory Arrest	0	0	0	0	0	0	3 (0.6)	<0.001
Gastrointestinal Disorders	2 (7.7)	0.004	7 (8.5)	0.014	9 (8.3)	0.011	21 (4.2)	0.004
Small Intestinal Obstruction	0	0	4 (4.9)	0.004	4 (3.7)	0.003	4 (0.8)	<0.001
Distal Intestinal Obstruction Syndrome	1 (3.8)	0.002	1 (1.2)	<0.001	2 (1.9)	0.001	2 (0.4)	<0.001
Distal Ileal Obstruction Syndrome	0	0	2 (2.4)	0.002	2 (1.9)	0.001	1 (0.2)	<0.001
General Disorders and Administration Site Conditions	0	0	1 (1.2)	<0.001	1 (0.9)	<0.001	10 (2.0)	0.001
Pyrexia	0	0	0	0	0	0	3 (0.6)	<0.001
Infections and Infestations	0	0	5 (6.1)	0.005	5 (4.6)	0.003	27 (5.5)	0.004
Device-Related Infection	0	0	1 (1.2)	<0.001	1 (0.9)	<0.001	3 (0.6)	<0.001
Influenza	0	0	0	0	0	0	4 (0.8)	<0.001
Renal and Urinary Disorders	0	0	0	0	0	0	10 (2.0)	0.001
Renal Failure Acute	0	0	0	0	0	0	5 (1.0)	<0.001
Nephrolithiasis	0	0	0	0	0	0	3 (0.6)	<0.001
Respiratory, Thoracic, and Mediastinal Disorders	20 (76.9)	0.128	65 (79.3)	0.167	85 (78.7)	0.155	250 (50.5)	0.084
Lung Disorder	19 (73.1)	0.120	61 (74.4)	0.151	80 (74.1)	0.141	221 (44.6)	0.071
Haemoptysis	0	0	5 (6.1)	0.005	5 (4.6)	0.004	26 (5.3)	0.004
Pneumonia	0	0	1 (1.2)	<0.001	1 (0.9)	<0.001	13 (2.6)	0.002
Infective Pulmonary Exacerbation of Cystic Fibrosis	0	0	2 (2.4)	0.002	2 (1.9)	0.001	10 (2.0)	0.002
Pneumothorax	1 (3.8)	0.002	1 (1.2)	<0.001	2 (1.9)	0.001	8 (1.6)	0.001
Respiratory Failure	0	0	2 (2.4)	0.002	2 (1.9)	0.001	5 (1.0)	<0.001
Chronic Sinusitis	0	0	1 (1.2)	<0.001	1 (0.9)	<0.001	5 (1.0)	<0.001
Cystic Fibrosis Lung	1 (3.8)	0.002	0	0	1 (0.9)	<0.001	4 (0.8)	<0.001
Acute Respiratory Failure	0	0	0	0	0	0	4 (0.8)	<0.001
Bronchopneumonia	1 (3.8)	0.002	2 (2.4)	0.002	3 (2.8)	0.002	0	0
Pneumonia Bacterial	0	0	0	0	0	0	3 (0.6)	<0.001
Surgical and Medical Procedures	1 (3.8)	0.002	0	0	1 (0.9)	<0.001	5 (1.0)	<0.001
Antibiotic Prophylaxis	1 (3.8)	0.002	0	0	1 (0.9)	<0.001	3 (0.6)	<0.001

Subjects are counted once only for each SOC and preferred term.

a Denominator for percentages is the number of subjects in the safety analysis set.

b Rate is adjusted for duration on study, which is defined as total number of days on study divided by 28.

Source: Section 11.1, Tables 5.3.1.2 – 5.3.1.5

Hospitalizations

A total of 358 subjects (59.4%) experienced 1016 hospitalizations (both treatment-emergent and nontreatment-emergent). In the < 18 year age group, 87 subjects (80.6%) were hospitalized compared to 271 subjects (54.7%) in the ≥ 18 year age group. Overall, the hospitalization rate per subject year was 1.4 (1.7 for subjects 6 to 12 years of age, 2.5 for subjects 13 to 17 years of age, 2.3 for subjects < 18 years of age, and 1.3 for subjects ≥ 18 years of age).

Table 21: EA-US-205-0111: Hospitalizations by Age Group (Safety Analysis Set)

	6 to 12 years (N = 26)	13 to 17 years (N = 82)	< 18 years (N=108)	≥ 18 years (N=495)
Number of Subjects Hospitalized, n (%)	20 (76.9)	67 (81.7)	87 (80.6)	271 (54.7)
Number of Hospitalizations	63	215	278	738
Number of Subjects Years Hospitalized	37.2	85.0	122.1	583.8
Hospitalization Rate per Subject Year	1.7	2.5	2.3	1.3

Source: Section 11.1, Tables 5.7.2 – 5.7.5

Comment:

EA-US-205-0111 was a compassionate-use programme in which no efficacy data were collected. 495 adults, 26 children 6-12 years and 82 children 13-17 years were included. Although Study EA-US-205-0111 was not included in the agreed AZLI Paediatric Investigation Plan (PIP; EMEA-000827-PIP01-09), the results were submitted as supportive data by the MAH.

Serious adverse events were similar across age groups with the exception of lung disorders which was reported with higher incidence among subjects < 18 years of age (74.1% <18 years versus 44.6% in adults). This may reflect the current standard of care in which pulmonary exacerbations in paediatric patients are more likely to be reported and treated compared to adults.

Haemoptysis was reported in similar frequencies in children and adults (4.6% versus 5.3%).

More children were hospitalised (80.6%) compared to adults (54.7%). Hospitalisation rate per subject was 2.3 for children compared to adults 1.3.

Summary of Serious Adverse Events Data

The SAE data from Study GS-US-205-0110 are consistent with results from the previously reported Phase 2/3 clinical studies of AZLI (Studies CP-AI-003, CP-AI-005, CP-AI-006, CP-AI-007, and GS-US-205-0117) and support the use of Cayston in all patients (including paediatrics ≥ 6 years of age) over repeated courses of treatment. In the randomised phase, a similar percentage of subjects reported SAEs in the AZLI-treated and the TNS-treated groups. In the extension phase, rates of SAEs did not increase with increased exposure to AZLI, and no differences in safety profiles were observed when subjects treated with TNS switched to AZLI.

Most of the SAEs that have occurred in adult and paediatric patients during clinical studies of AZLI were attributable to pulmonary exacerbations; the most common SAE reported in both age groups was cough. Cayston continues to be a generally well-tolerated and effective inhaled antipseudomonal antibiotic therapy for both adults and children aged 6 years and older over multiple treatment courses.

Paediatric Deaths

No paediatric patients died during Phase 2/3 clinical studies of AZLI. However, in Study EA US 205-0111 a total of 33 subjects (5.5%) died on study (post-baseline visit), including 1 subject (3.8%) in the 6 to 12 year age group, 3 subjects (3.7%) in the 13 to 17 year age group, and 29 subjects in the ≥ 18 year age group, respectively. five paediatric patients died after screening.

All deaths were reported not to be related to AZLI.

Laboratory findings

Not applicable

Safety in special populations

Not applicable

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to AES

Four patients in the placebo controlled studies [two placebo and two AZLI treated patients (1 rash, urticaria, dizziness and 1 headache)] discontinued because of study drug intolerance. In the open follow on study 2 and 5 patients in the AZLI BID and AZLI TID groups respectively discontinued because of study drug intolerance (mostly due to chest or lung function AE and single case of tinnitus, arthralgia or hemoptysis.

Study GS-US-205-0110, Randomised Phase

There were 9 subjects (6.6%) treated with AZLI and 1 subject (0.8%) treated with TNS who discontinued study drug due to AEs. Six subjects (4.4%) treated with AZLI and 1 subject (0.8%) treated with TNS discontinued due to respiratory AEs, most frequently productive cough and hemoptysis (AZLI: 3 subjects (2.2%), TNS: 0 subjects for each PT). Additional respiratory events experienced by the 6 AZLI-treated subjects included dyspnea (2 SAEs), oropharyngeal pain (1 AE, 1 SAE), bronchial secretion retention (1 AE), cough (2 SAEs), rales (1 SAE), sputum discolored (1 SAE), and wheezing (1 SAE). The 1 TNS-treated subject who withdrew experienced fatigue, rhinorrhea, and oropharyngeal pain.

The CHMP commented on the higher rates of patients reporting drug-related AEs (including severe AEs and discontinuations) in the AZLI group after 3 courses of treatment in their Request for Supplementary Information (Question 3) dated 22 December 2010 (EMA Ref. EMA/841208/2010). Gilead responded stating that the Data Safety Monitoring Committee had evaluated the safety data during the trial and did not recommend any changes and that placebo-controlled studies of AZLI are the most informative with regard to evaluating drug-related AEs. Full details can be found in Gilead's response to the CHMP Request for Supplementary Information (Question 3) submitted on 16 March 2011 and this question was deemed resolved in the Specific Obligation assessment report dated 17 June 2011.

Study GS-US-205-0110, Extension Phase

One subject (1.5%) in the AZLI/AZLI treatment group and 5 subjects (7.7%) in the TNS/AZLI treatment group discontinued study drug due to AEs. Three of the TNS/AZLI-treated subjects and the 1 AZLI/AZLI-treated subject discontinued due to AEs assessed by the investigator as related to study drug. The AZLI/AZLI-treated subject experienced 2 events of pyrexia (mild) and 1 event of fatigue (mild). Two subjects (3.1%) in the TNS/AZLI treatment group discontinued due to respiratory AEs (bronchial obstruction [moderate] and productive cough [severe]). The subject who experienced bronchial obstruction also experienced a moderate decrease in exercise tolerance (1.5%). Two subjects (3.1%) in the TNS/AZLI treatment group experienced tongue disorder (mild), 1 of these subjects also experienced oral discomfort (mild) and the other subject also experienced mouth ulcerations (mild), diarrhea (mild), lip swelling (mild), dysgeusia (mild), and vaginal haemorrhage (mild). One subject in the TNS/AZLI treatment group experienced decreased pulmonary function test (severe).

Expanded Access Programme, Protocol EA-US-205-0111

In study EA-US-205-011 lung disorder was the most frequent SAE leading to discontinuation (29 subjects [4.8%]).

Expanded Access Programme (Protocol EA-US-205-0122)

As of 06 July 2011, 2 subjects (5.7%) have discontinued study drug as a result of SAEs (chronic respiratory failure and lung infection "pseudomonal" in Subject 406-12 and lung disorder in Subject 410-02). The SAEs for both subjects were assessed by the investigator as not being related to study drug.

Comment:

Data from the overall patient population suggests that AZLI is well tolerated. Discontinuation was caused due to pulmonary disorders. No specific paediatric data was submitted by the MAH.

Microbiology and resistance

MIC_{50} and MIC_{90} values PA isolates

MIC_{50} and MIC_{90} values PA isolates, GS-US-205-0110 randomised phase

The MIC_{50} (the minimum concentration of an agent that inhibits 50% of isolates from a particular organism) and MIC_{90} (the minimum concentration of an agent that inhibits 90% of isolates from a particular organism) of aztreonam for all PA isolates in the randomised phase of the study are presented in Table 22. The aztreonam MIC_{50} for all PA isolates was identical at baseline (2 μg/mL) and remained unchanged (≤ 2-fold changes) in both treatment groups throughout the study. There was a 4-fold difference at baseline in the aztreonam MIC_{90} for all PA isolates between the AZLI treatment group (32 μg/mL) and the TNS (128 μg/mL) treatment group. The aztreonam MIC_{90} remained unchanged (≤ 2-fold changes) in the TNS treatment group throughout the study. In the AZLI treatment group, persistent increases in the aztreonam MIC_{90} were observed. At the end of study (Week 24), however, the aztreonam MIC_{90} in the AZLI treatment group (128 μg/mL) was within a 2-fold difference of the TNS treatment group (64 μg/mL).

Table 22: GS-US-205-0110, Randomised Phase: MIC_{50} and MIC_{90} of Aztreonam for All *PA* Isolates (μg/mL) (Safety Population)

Treatment	Week	n[a]	MIC_{50}	MIC_{90}	Min	Max	Change in MIC_{50}	Change in MIC_{90}
AZLI (N = 136)	0	208	2	32	≤ 1	> 2048		
	2	200	2	64	≤ 1	> 2048	unchanged	unchanged
	4	198	4	128	≤ 1	> 2048	unchanged	increased
	8	201	4	64	≤ 1	> 2048	unchanged	unchanged
	12	205	4	128	≤ 1	> 2048	unchanged	increased
	16	191	4	128	≤ 1	> 2048	unchanged	increased
	20	199	4	128	≤ 1	2048	unchanged	increased
	24	206	2	128	≤ 1	> 2048	unchanged	increased
TNS (N = 132)	0	198	2	128	≤ 1	2048		
	2	179	2	64	≤ 1	256	unchanged	unchanged
	4	191	2	64	≤ 1	> 2048	unchanged	unchanged
	8	196	≤ 1	64	≤ 1	1024	unchanged	unchanged
	12	170	2	64	≤ 1	2048	unchanged	unchanged
	16	160	2	64	≤ 1	512	unchanged	unchanged
	20	163	≤ 1	64	≤ 1	1024	unchanged	unchanged
	24	169	2	64	≤ 1	1024	unchanged	unchanged

Change categories: "Increased is defined as ≥ 4-fold increase in MIC, "Unchanged" is defined as MIC values ± a 2-fold change, "Decreased" is defined as ≥ 4-fold decrease in MIC.
a n = the number of isolates

In contrast, the tobramycin MIC_{50} (2 μg/mL) and MIC_{90} (64 μg/mL) for all *PA* isolates were identical at baseline between the AZLI and TNS treatment groups. The tobramycin MIC_{50} and MIC_{90} remained unchanged (≤ 2 fold changes) among TNS-treated subjects throughout the study, and decreased 4-fold at 2 visits among AZLI-treated subjects (Weeks 2 and 12).

The change from baseline in the MIC of **aztreonam** for the least susceptible *PA* isolate to aztreonam from each subject is presented for each visit in Table 23. The MIC for the least susceptible *PA* isolate to aztreonam remained unchanged (≤ 2-fold increase/decrease) in 52% to 58% of AZLI-treated subjects and 53% to 67% of TNS-treated subjects from Week 2 to 24. Throughout the study, the MIC for the least susceptible *PA* isolate to aztreonam increased ≥ 4-fold in 26% to 35% of AZLI-treated subjects compared to 11% to 21% of TNS-treated subjects. Throughout the study, the MIC for the least susceptible *PA* isolate to aztreonam decreased ≥ 4-fold in 11% to 16% of AZLI-treated subjects compared to 19% to 26% of TNS-treated subjects. These differences achieved statistical significance at Weeks 8, 12, 16, 20, and 24 ($p < 0.05$).

Table 23: GS-US-205-0110: Change in MIC of Aztreonam from Baseline for *PA* Isolate with the Highest MIC from Each Subject (Safety Population)

Visit	Week	AZLI (N=136)	TNS (N=132)
Week 24/Visit 9 (End of off treatment)	n[a]	102	89
	MIC Increased[b]	36 (35.3)	13 (14.6)
	MIC Unchanged[c]	53 (52.0)	56 (62.9)
	MIC Decreased[d]	13 (12.7)	20 (22.5)
	p-value[e]	0.001	

a n = the number of subjects with available data
b subjects with ≥ 4-fold increase in MIC
c subjects with MIC values ± a 2-fold change
d subjects with ≥ 4-fold decrease in MIC
e comparisons are based on CMH (row mean score) test

The change from baseline in the MIC of **tobramycin** for the least susceptible *PA* isolate to tobramycin from each subject is presented in Table 24. The MIC of tobramycin remained unchanged (≤ 2-fold increase/decrease) in 68% to 76% of AZLI-treated subjects and 60% to 69% of TNS-treated subjects from Weeks 2 to 24. Throughout the study, the MIC for the least susceptible *PA* isolate to tobramycin increased ≥ 4-fold in 15% to 28% of TNS-treated subjects compared to 8% to 13% of AZLI-treated subjects. At the end of all treatment courses, the MIC for the least susceptible *PA* isolate to tobramycin decreased ≥ 4-fold in 19% to 24% of AZLI-treated subjects compared to 12% to 14% of TNS-treated subjects. These differences achieved statistical significance at Weeks 12 and 20 and approached statistical significance at the end of the study (Week 24: p = 0.052).

Table 24: GS-US-205-0110: Change in MIC of Tobramycin from Baseline for *PA* Isolate with the Highest MIC from Each Subject (Safety Population)

Visit	Week	AZLI (N=136)	TNS (N=132)
Week 24/Visit 9 (End of off treatment)	n[a]	102	89
	MIC Increased[b]	11 (10.8)	18 (20.2)
	MIC Unchanged[c]	72 (70.6)	60 (67.4)
	MIC Decreased[d]	19 (18.6)	11 (12.4)
p-value[e]		0.052	

a n = the number of subjects with available data
b subjects with ≥ 4-fold increase in MIC
c subjects with MIC values ± a 2-fold change
d subjects with ≥ 4-fold decrease in MIC
e comparisons are based on CMH (row mean score) test

Comment:

Of concern are the observed increases (4-fold) in the MIC_{90} of aztreonam for all PA isolates in the AZLI treatment group, from baseline 32 µg/ml to 128 µg/ml at week 24. In contrast MIC90 for TNS decreased from 128 µg/ml at baseline to 64 µg/ml at week 24.

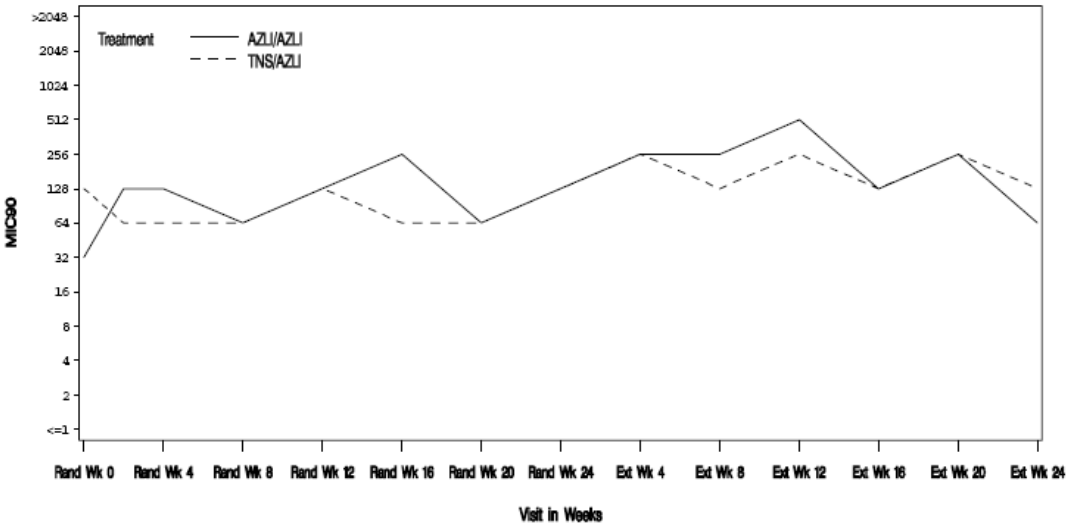
Similarly, the increases (4-fold) in the MIC for the least susceptible PA isolate to aztreonam in the AZLI-treated patients are of concern. A 4-fold increase in MIC for aztreonam in the least susceptible PA isolate was reported for 35% of subjects at week 24, whereas in the TNS group only 20% of subjects that were exposed to tobramycin demonstrated a 4-fold increase in MIC for tobramycin.

Similar effects in the AZLI group were observed when the established parenteral resistance breakpoint for aztreonam (MIC >8 µg/mL) was considered in the analysis: At baseline, 39 AZLI-treated patients (34%) and 38 TNS-treated patients (35%) had a PA isolate with aztreonam MIC >8 µg/mL. At the end of the first course of treatment (Week 4), 45 AZLI-treated patients (40%) had a PA isolate with aztreonam MIC >8 µg/mL. Throughout the study, this percentage remained above the baseline value. At Week 24, 56 patients (49%) treated with AZLI had a PA isolate with aztreonam MIC > 8 µg/mL. In the TNS group the percentage of patients with PA isolate with aztreonam MIC > 8 µg/mL remained below the baseline value after the first course, ranging from 26% to 32%.

MIC_{50} and MIC_{90} of Aztreonam and Tobramycin for all PA Isolates, GS-US-205-0110 overall study

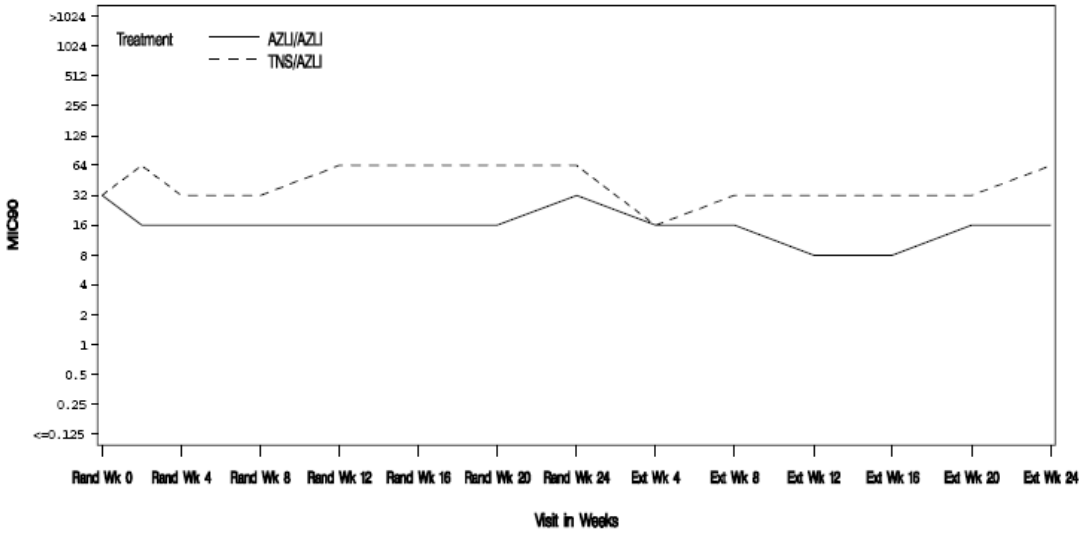
There was a ≥2-fold difference at Randomized Week 0 in the **aztreonam** MIC_{50} for all PA isolates between the AZLI/AZLI (2 µg/mL) and TNS/AZLI (≤1 µg/mL) treatment groups as well as a 4-fold difference at baseline in the aztreonam MIC_{90} between the AZLI/AZLI (32 µg/mL) and TNS/AZLI (128 µg/mL) treatment groups. During the randomised phase, the aztreonam MIC_{50} for all PA isolates remained unchanged (≤ 2-fold changes) in the AZLI/AZLI and TNS/AZLI treatment groups. During the extension phase, the aztreonam MIC_{50} for all PA isolates remained unchanged (≤ 2-fold changes) in the TNS/AZLI treatment group. Three intermittent increases (4-fold changes) in the aztreonam MIC_{50} were observed over the 12-month study in the AZLI/AZLI treatment group. However, at Extension Week 24, the aztreonam MIC_{50} remained unchanged (≤ 2-fold change) from Randomised Week 0. During the randomised phase, the aztreonam MIC_{90} for all PA isolates increased (≥ 4-fold changes) 5 times in the AZLI/AZLI treatment groups and remained unchanged (≤ 2-fold changes) in the TNS/AZLI treatment group. During the extension phase, the aztreonam MIC_{90} for all PA isolates remained unchanged (≤ 2-fold changes) in the TNS/AZLI treatment group. Frequent increases (≥4-fold changes) in the aztreonam MIC_{90} were observed in the study overall for the AZLI/AZLI treatment group. However, at Extension Week 24, the aztreonam MIC_{90} remained unchanged (≤ 2-fold change) from Randomised Week 0.

Figure 2: GS-US-205-0110 Study Overall: MIC_{90} of Aztreonam for all *PA* Isolates



There was a 2-fold difference at Randomised Week 0 in the **tobramycin** MIC_{50} for all *PA* isolates between the AZLI/AZLI (1 µg/mL) and TNS/AZLI (2 µg/mL) treatment groups but no difference at baseline in the aztreonam MIC_{90} (32 µg/mL) between the AZLI/AZLI and TNS/AZLI treatment groups. During the randomised phase, the tobramycin MIC_{50} and MIC_{90} for all *PA* isolates remained unchanged (≤ 2-fold changes) in the AZLI/AZLI and TNS/AZLI treatment groups. During the extension phase in the TNS/AZLI treatment group (when the subjects were treated with AZLI), the tobramycin MIC_{50} for all *PA* isolates remained unchanged (≤ 2-fold changes) while a single 4-fold decrease in tobramycin MIC_{90} was observed at Extension Week 4. In the AZLI/AZLI treatment group, the tobramycin MIC_{50} and MIC_{90} remained unchanged for the study overall, while two 4-fold decreases in the tobramycin MIC_{90} were observed at Extension Weeks 12 and 16.

Figure 3: GS-US-205-0110 Study Overall: MIC_{90} of Tobramycin for all *PA* Isolates



Comment:

The increased MIC_{90} in the AZLI group remained elevated in the extension phase, whereas the initial MIC_{90} for Aztreonam also showed a general increase without further linear progression during the extension phase with AZLI in subjects initially treated with TNS.

The percentage increased MIC_{50} to aztreonam remained the same during the randomisation period and during the extension period in both groups TNS/AZLI and AZLI/AZLI.

The increase in MIC_{90} in the AZLI group - as observed during the 24 weeks of the randomisation period - remained elevated in the extension phase in the AZLI/AZLI group. In the TNS/AZLI group the initial MIC_{90} for Aztreonam also showed a mild increase during the extension phase in which AZLI was administered to subjects initially treated with TNS.

During the extension period the MIC_{90} of tobramycin remained unchanged.

Relevant species

Pseudomonas aeruginosa

Ninety-seven percent (97.0%) of AZLI-treated subjects and 92.3% of TNS-treated subjects tested positive for PA at Week -2 and/or Week 0 (baseline) (Table 22). Of the 14 subjects who tested negative for PA at baseline [AZLI (n=4); TNS (n=10)], all but 4 TNS-treated subjects tested positive for PA at one or more visits during the study. Of the AZLI-treated subjects (n=128) and TNS-treated subjects (n=120) who tested positive for PA at baseline, 23 (18.0%) and 27 (22.5%) tested negative for PA at one or more visits during the study (Weeks 2-24). Disappearance data was not available for one TNS-treated subject. Study inclusion criteria were designed to guide enrolment of subjects with chronic PA infection. Subjects who tested negative for PA at baseline or during the study may be more reflective of poor sputum sampling than true absence of the pathogen. Further, eradication of PA is not expected in subjects with chronic infection.

Table 25: GS-US-205-0110, Randomised Phase: Presence or Absence of *PA* by Visit (Safety Population)

			Presence and Disappearance			**Absence and Appearance**		
Pathogen	**Week**	**n[a]**	**Presence n[b] (%)**	**Disappear n (%)**	**No Change n (%)**	**Absence n[c] (%)**	**Appear n (%)**	**No Change n (%)**
AZLI (N = 136)	-2 / 0	132	128[b] (97.0)			4[c] (3.0)		
	2	124	112 (90.3)	10 (7.8)	109 (85.2)	12 (9.7)	2 (50.0)	2 (50.0)
	4	129	117 (90.7)	11 (8.6)	112 (87.5)	12 (9.3)	3 (75.0)	1 (25.0)
	8	126	116 (92.1)	7 (5.5)	113 (88.3)	10 (7.9)	1 (25.0)	3 (75.0)
	12	126	115 (91.3)	9 (7.0)	110 (85.9)	11 (8.7)	2 (50.0)	2 (50.0)
	16	119	109 (91.6)	8 (6.3)	106 (82.8)	10 (8.4)	2 (50.0)	2 (50.0)
	20	119	111 (93.3)	5 (3.9)	108 (84.4)	8 (6.7)	1 (25.0)	3 (75.0)
	24	126	115 (91.3)	9 (7.0)	112 (87.5)	11 (8.7)	1 (25.0)	2 (50.0)

	2 - 24			23 (18.0)	105 (82.0)		4 (100.0)	0
TNS (N = 132)	-2 / 0	130	120[b] (92.3)			10[c] (7.7)		
	2	123	106 (86.2)	9 (7.5)	102 (85.0)	17 (13.8)	3 (30.0)	7 (70.0)
	4	125	109 (87.2)	8 (6.7)	106 (88.3)	16 (12.8)	2 (20.0)	8 (80.0)
	8	122	114 (93.4)	3 (2.5)	107 (89.2)	8 (6.6)	5 (50.0)	5 (50.0)
	12	115	100 (87.0)	8 (6.7)	95 (79.2)	15 (13.0)	3 (30.0)	7 (70.0)
	16	110	95 (86.4)	9 (7.5)	91 (75.8)	15 (13.6)	3 (30.0)	6 (60.0)
	20	106	93 (87.7)	8 (6.7)	89 (74.2)	13 (12.3)	3 (30.0)	5 (50.0)
	24	113	97 (85.8)	11 (9.2)	93 (77.5)	16 (14.2)	3 (30.0)	5 (50.0)
	2 - 24			27 (22.5)	92 (76.7)		6 (60.0)	4 (40.0)

a n = the number of subjects with available data
b n used as denominator for "disappearance" and associated "no change"
c n used as denominator for "appearance" and associated "no change"

Comment:

Based on the table above it is shown that patients treated with AZLI have a decrease in presence of PA from baseline (week -2) 97.0% to 91.3% in week 24. Patients treated with TNS showed a reduction in PA from baseline (week -2) 92.3% to 85.8% in week 24. These data demonstrate once more that in most CF patients chronic infection with PA cannot be eradicated by inhalation of antibiotics, but that bacterial load reductions of PA by suppressive antibiotic therapy may at most prevent exacerbations and reduce the rate of progressive decline of lung function. Considering this lack of eradication and the decrease in susceptibility to aztreonam in the persistent bacteria colonizing the airways, patients end up with resistant PA.

Methicillin-Sensitive Staphylococcus aureus (MSSA)

Thirty-six percent (36.4%) of AZLI-treated subjects and 39.2% of TNS-treated subjects tested positive for MSSA at Week -2 and/or Week 0 (baseline) (table 23). Of the 48 AZLI-treated subjects and 51 TNS-treated subjects with MSSA present at baseline, 25 (52.1%) and 30 (58.8%), respectively, tested negative for MSSA at 1 or more visits during the study (Weeks 2-24). Of the 84 AZLI-treated subjects with a negative culture for MSSA at Week -2 and Week 0, 22 (26.2%) were culture positive at 1 or more visits throughout the study, while 62 (73.8%) remained culture negative throughout the study. Of the 79 TNS-treated subjects with a negative culture for MSSA at Week -2 and Week 0, 15 (19.0%) were culture positive at 1 or more visits throughout the study, while 63 (79.7%) remained culture negative throughout the study. Appearance data was not available for 1 TNS-treated subject.

Table 26: GS-US-205-0110: Presence or Absence of MSSA by Visit (Safety Population)

Pathogen	Week	n[a]	Presence and Disappearance			Absence and Appearance		
			Presence n[b] (%)	Disappear n (%)	No Change n (%)	Absence n[c] (%)	Appear n (%)	No Change n (%)
AZLI (N = 136)	-2 / 0	132	48[b] (36.4)			84[c] (63.6)		
	2	124	39 (31.5)	10 (20.8)	36 (75.0)	85 (68.5)	2 (2.4)	75 (89.3)
	4	129	37 (28.7)	13 (27.1)	32 (66.7)	92 (71.3)	4 (4.8)	78 (92.9)
	8	126	46 (36.5)	9 (18.8)	36 (75.0)	80 (63.5)	9 (10.7)	70 (83.3)
	12	126	40 (31.7)	12 (25.0)	32 (66.7)	86 (68.3)	7 (8.3)	72 (85.7)
	16	119	47 (39.5)	11 (22.9)	33 (68.8)	72 (60.5)	14 (16.7)	60 (71.4)
	20	119	44 (37.0)	10 (20.8)	32 (66.7)	75 (63.0)	12 (14.3)	63 (75.0)
	24	126	40 (31.7)	13 (27.1)	30 (62.5)	86 (68.3)	9 (10.7)	72 (85.7)
	2 - 24			25 (52.1)	23 (47.9)		22 (26.2)	62 (73.8)
TNS (N = 132)	-2 / 0	130	51[b] (39.2)			79[c] (60.8)		
	2	123	38 (30.9)	11 (21.6)	36 (70.6)	85 (69.1)	1 (1.3)	73 (92.4)
	4	125	36 (28.8)	17 (33.3)	33 (64.7)	89 (71.2)	3 (3.8)	71 (89.9)
	8	122	41 (33.6)	17 (33.3)	31 (60.8)	81 (66.4)	8 (10.1)	64 (81.0)
	12	115	35 (30.4)	14 (27.5)	31 (60.8)	80 (69.6)	3 (3.8)	65 (82.3)
	16	110	36 (32.7)	15 (29.4)	30 (58.8)	74 (67.3)	5 (6.3)	59 (74.7)
	20	106	33 (31.1)	12 (23.5)	29 (56.9)	73 (68.9)	3 (3.8)	61 (77.2)
	24	113	35 (31.0)	15 (29.4)	31 (60.8)	78 (69.0)	3 (3.8)	63 (79.7)
	2 - 24			30 (58.8)	21 (41.2)		15 (19.0)	63 (79.7)

a n = the number of subjects with available data
b n used as denominator for "disappearance" and associated "no change"
c n used as denominator for "appearance" and associated "no change"

Table 27: GS-US-205-0110 Study Overall: Presence and Absence of MSSA (Safety Population)

Randomized Week/ Extension Week	AZLI/AZLI (N = 68)			TNS/AZLI (N = 65)		
	n[a]	Presence n (%)	Absence n (%)	n[a]	Presence n (%)	Absence n (%)
Randomized Week -2	63	18 (28.6)	45 (71.4)	63	24 (38.1)	39 (61.9)
Randomized Week 0	63	22 (34.9)	41 (65.1)	61	27 (44.3)	34 (55.7)
Randomized Weeks -2 and 0	67	24 (35.8)	43 (64.2)	64	28 (43.8)	36 (56.3)
Randomized Week 2	64	21 (32.8)	43 (67.2)	60	24 (40.0)	36 (60.0)
Randomized Week 4	66	19 (28.8)	47 (71.2)	64	23 (35.9)	41 (64.1)
Randomized Week 8	66	29 (43.9)	37 (56.1)	64	26 (40.6)	38 (59.4)
Randomized Week 12	65	24 (36.9)	41 (63.1)	61	23 (37.7)	38 (62.3)
Randomized Week 16	63	29 (46.0)	34 (54.0)	60	24 (40.0)	36 (60.0)
Randomized Week 20	64	28 (43.8)	36 (56.3)	58	20 (34.5)	38 (65.5)
Randomized Week 24	66	24 (36.4)	42 (63.6)	58	21 (36.2)	37 (63.8)
Randomized Weeks 2-24	68	39 (57.4)	29 (42.6)	65	37 (56.9)	28 (43.1)
Extension Week 0	63	24 (38.1)	39 (61.9)	54	18 (33.3)	36 (66.7)
Extension Week 4	64	25 (39.1)	39 (60.9)	60	24 (40.0)	36 (60.0)
Extension Week 8	59	23 (39.0)	36 (61.0)	58	20 (34.5)	38 (65.5)
Extension Week 12	56	19 (33.9)	37 (66.1)	55	24 (43.6)	31 (56.4)
Extension Week 16	55	17 (30.9)	38 (69.1)	55	24 (43.6)	31 (56.4)
Extension Week 20	56	16 (28.6)	40 (71.4)	53	19 (35.8)	34 (64.2)
Extension Week 24	60	20 (33.3)	40 (66.7)	56	24 (42.9)	32 (57.1)
Extension Weeks 4-24	67	36 (53.7)	31 (46.3)	65	33 (50.8)	32 (49.2)
Randomized Weeks 2 - Extension Weeks 24	68	43 (63.2)	25 (36.8)	65	40 (61.5)	25 (38.5)

All subjects were treated with AZLI during the extension phase of the study.
Most subjects attended Randomized Week 24 and Extension Week 0 visits on the same day and thus have identical data values summarized at both visits.
For a defined period, a pathogen was counted as being present if there was ever a positive isolation detected. Presence at multiple visits was counted only once.
For a defined period, a pathogen was counted as being absent if there was never a positive isolation detected.
n = the number of subjects with available data at each visit and was used as the denominator for the calculation of percentage.

Comment:

In the randomised phase of GS-US-205-0110 (Table 26) both the AZLI- and TNS-treated patient groups showed reductions in the presence of MSSA from baseline (week -2) till week 24. In the AZLI group a reduction from 36.4% to 31.7% was shown versus a reduction in the TNS group 39.2% to 31.0%.

In the extension phase all patients were switched on AZLI, either after AZLI pre-treatment (AZLI/AZLI) or after TNS pre-treatment (TNS/AZLI). In AZLI/AZLI, MSSA remained present in about one third of all subjects both at the end of the randomisation period of 24 weeks and after conclusion of the extension period of 24 weeks. However, an increase in the presence of MSSA was seen in the extension phase

(table 27) for TNS/AZLI patients (n=65) from 36.2% at week 24 of the TNS treatment period to 42.9% in extension period at week 24 after treatment with AZLI.

Methicillin-Resistant Staphylococcus aureus (MRSA)

Seventeen percent (17.4%) of AZLI-treated subjects and 20.0% of TNS-treated subjects tested positive for MRSA at Week -2 and/or Week 0 (baseline) (table 28). Of the 23 AZLI-treated subjects and 26 TNS-treated subjects with MRSA present at baseline, 9 (39.1%) and 13 (50.0%), respectively, tested negative for MRSA at 1 or more visits during the study (Week 2-24). Of the 109 AZLI-treated subjects with a negative culture for MRSA at Week -2 and Week 0, 13 (12%) were culture positive at 1 or more visits throughout the study, while 96 (88.1%) remained culture negative throughout the study. Of the 104 TNS-treated subjects with a negative culture for MRSA at Week -2 and Week 0, 1 (1.0%) was culture positive at 1 or more visits throughout the study, while 102 (98.1%) remained culture negative throughout the study. Appearance data was not available for 1 TNS-treated subject. The percentage of AZLI-treated subjects with a positive culture for MRSA remained relatively constant (16 to 20%) from Weeks 2 to 24 and similar to the baseline (Week -2/0) value (17%). The percentage of TNS-treated subjects with a positive culture for MRSA remained relatively constant (11 to 16%) from Weeks 2 to 24 but was always lower than the baseline value (20%).

Table 28: GS-US-205-0110: Presence or Absence of MRSA by Visit (Safety Population)

			Presence and Disappearance			**Absence and Appearance**		
Pathogen	**Week**	**n[a]**	**Presence n[b] (%)**	**Disappear n (%)**	**No Change n (%)**	**Absence n[c] (%)**	**Appear n (%)**	**No Change n (%)**
AZLI (N = 136)	-2 / 0	132	23[b] (17.4)			109[c] (82.6)		
	2	124	20 (16.1)	2 (8.7)	18 (78.3)	104 (83.9)	2 (1.8)	101 (92.7)
	4	129	25 (19.4)	1 (4.3)	22 (95.7)	104 (80.6)	3 (2.8)	101 (92.7)
	8	126	21 (16.7)	5 (21.7)	17 (73.9)	105 (83.3)	4 (3.7)	98 (89.9)
	12	126	21 (16.7)	6 (26.1)	15 (65.2)	105 (83.3)	6 (5.5)	96 (88.1)
	16	119	20 (16.8)	4 (17.4)	16 (69.6)	99 (83.2)	4 (3.7)	94 (86.2)
	20	119	21 (17.6)	6 (26.1)	15 (65.2)	98 (82.4)	6 (5.5)	90 (82.6)
	24	126	25 (19.8)	4 (17.4)	18 (78.3)	101 (80.2)	7 (6.4)	95 (87.2)
	2 - 24			9 (39.1)	14 (60.9)		13 (11.9)	96 (88.1)
TNS (N =132)	-2 / 0	130	26[b] (20.0)			104[c] (80.0)		
	2	123	16 (13.0)	8 (30.8)	16 (61.5)	107 (87.0)	0 (0.0)	97 (93.3)
	4	125	20 (16.0)	5 (19.2)	20 (76.9)	105 (84.0)	0 (0.0)	99 (95.2)
	8	122	18 (14.8)	8 (30.8)	17 (65.4)	104 (85.2)	1 (1.0)	94 (90.4)
	12	115	17 (14.8)	5 (19.2)	17 (65.4)	98 (85.2)	0 (0.0)	91 (87.5)
	16	110	17 (15.5)	4 (15.4)	16 (61.5)	93 (84.5)	1 (1.0)	88 (84.6)
	20	106	17 (16.0)	4 (15.4)	16 (61.5)	89 (84.0)	1 (1.0)	84 (80.8)
	24	113	12 (10.6)	8 (30.8)	12 (46.2)	101 (89.4)	0 (0.0)	92 (88.5)
	2 - 24			13 (50.0)	13 (50.0)		1 (1.0)	102 (98.1)

a n = the number of subjects with available data
b n used as denominator for "disappearance" and associated "no change"
c n used as denominator for "appearance" and associated "no change"

Treatment-emergent Isolation of MRSA was more pronounced in AZLI treated patients compared to TNS (AZLI 6.8% versus TBS 0.8%).

Comment:

The treatment emerging isolation of MRSA was most pronounced in the AZLI group: 17% of subjects isolated MRSA at baseline and 20% at week 24, whereas in the TNS group the proportion dropped from 20% at baseline to 11% at week 24 of TNS treatment. In 12% of AZLI patients this pathogen appeared during the study period, whereas it was only newly isolated in 1% of the TNS-treated subjects.

The isolation of MRSA in increasing numbers of AZLI patients is worrisome, because MRSA will result in increased disease severity (Sawicki, Pediatr Pulmonol, 2008) and is associated with decreased survival. The attributable risk of death associated with MRSA was 34% in the trial of Dasenbrook, JAMA, 2010.

Temporary gains in FEV_1 while on treatment with AZLI might therefore be compromised in the near future by treatment-emerging MRSA, more frequent than with TNS, which is particularly worrisome because of the young age of these CF patients.

A warning referring to the association between persistent isolation of MRSA and worse clinical outcome, as reported in the literature, is added to the Product Information.

PA Resistance to Antibiotic Class

GS-US-205-0110 Randomised Phase

Subjects with MIC for *PA* greater than the parenteral breakpoint of amikacin, cefepime, ceftazidime, piperacillin, piperacillin/tazobactam, ticarcillin/clavulanic acid, meropenem and ciprofloxacin for their *PA* isolate with the highest MIC at each visit are presented in the Study GS-US-205-0110 CSR.

The 8 antibiotics listed in the paragraph above and tobramycin were grouped according to antibiotic class. Those subjects with MIC greater than the parenteral breakpoint of amikacin and tobramycin, 1 or more of the beta-lactams, all 6 beta-lactams, and ciprofloxacin (*PA* isolate with the highest MIC at each visit) were identified. In addition, subjects with multi-drug resistant *PA* (MDR*PA*) are presented according to two definitions: 1) subjects with at least 1 *PA* isolate resistant to all antibiotics tested in 2 of the 3 drug classes, and 2) subjects with at least 1 *PA* isolate resistant to at least 1 antibiotic tested in 2 of the 3 drug classes.

At baseline (Week 0), similar percentages of subjects in the AZLI and TNS treatment groups had *PA* isolates with antibiotic resistance to beta-lactams, aminoglycosides and quinolones. The percentage of subjects with at least one *PA* isolate resistant to 1 or more beta-lactams was nearly identical between treatment groups (AZLI: 64 subjects [55.7%], TNS: 63 subjects [57.3%]). The percentage of subjects with at least 1 *PA* isolate resistant to tobramycin and amikacin was nearly identical between treatment groups (AZLI: 36 [31.3%], TNS: 32 [29.1%]). Subjects with at least 1 *PA* isolate resistant to ciprofloxacin were nearly identical between treatment groups (AZLI: 68 [59.1%]; TNS: 63 [57.3%]). Subjects with at least 1 *PA* isolate resistant to all antibiotics tested in 2 of the 3 drug classes (Cystic Fibrosis Foundation definition of MDR*PA*) were nearly identical between treatment groups (AZLI: 35 [30.4]%; TNS: 35 [31.8%]) and subjects with at least 1 *PA* isolate resistant to at least 1 antibiotic tested in 2 of the 3 drug classes (alternate definition of MDR*PA*) were nearly identical between treatment groups (AZLI: 67 [58.3]%; TNS: 66 [60%]).

At the end of the first treatment course (Week 4) through Week 24, the percentage of subjects with at

least 1 *PA* isolate resistant to 1 or more beta-lactams increased from the baseline value (55.7%) to 61% to 72% and was 66.7% at Week 24. The percentage of TNS-treated subjects with at least 1 *PA* isolate resistant to 1 or more beta-lactams increased from the baseline value (57.3%) to 62.5% at the end of the first TNS treatment course, decreased at the end of the last treatment course to 47.8%, and returned to the baseline value at Week 24. At the end of the first and last AZLI courses, the percentage of subjects with at least 1 *PA* isolate resistant to all beta-lactams increased from the baseline value (13%) to 18% and 21%, respectively, and was 18.4% at Week 24. The percentage of TNS-treated subjects with at least 1 *PA* isolate resistant to all beta-lactams increased from the baseline value (17%) to 21% at the end of the first TNS treatment course but decreased at the end of the last treatment course to 12.3%. At the end of all 3 TNS treatment courses, the percentage of subjects with at least 1 *PA* isolate resistant to tobramycin and amikacin increased from the baseline value (29%) to 35% to 37%. At the end of all 3 AZLI treatment courses, the percentage of subjects with at least 1 *PA* isolate resistant to tobramycin and amikacin decreased from the baseline value (31%) to 21% to 27%. Throughout the study, the percentage of subjects in both treatment groups with at least 1 *PA* isolate resistant to ciprofloxacin remained similar to their baseline values.

Based on either definition of MDR*PA*, the percentage of subjects with MDR*PA* did not change throughout the study in either treatment group. The percentage of AZLI subjects with MDR*PA* ranged from 25% to 34% from Week 0 to 24 while the percentage of TNS-treated subjects with MDR*PA* ranged from 27% to 34%.

In their Request for Supplementary Information (Question 4c-d), dated 22 December 2010 (EMA Ref. EMA/841208/2010), the CHMP commented on the changes in the susceptibility of *PA* to cefepime and piperacillin in AZLI-treated subjects during the randomised phase, as well as increases in the percentage of AZLI-treated subjects with parenteral resistance to all beta-lactams during the randomised phase of the study. Gilead responded stating that cross-resistance to other antibiotics in the same class is a likely consequence of suppressive antibiotic therapy in which eradication of *PA* is unexpected, but that the data suggest that the availability of two inhaled antibiotics from different classes (AZLI and TNS) provides physicians with a means to better manage the development of resistance.

Comment:

Bêta lactam antibiotics, especially third generation cephalosporines, are frequently administered intravenously in case of pulmonary infections and especially in case of Pseudomonas infections. An increase in PA resistance rates to at least 1 beta lactam antibiotic during treatment was demonstrated in AZLI: from baseline (week 0/2) 55.7% to 66.7% in week 24, whereas in TNS this proportion remained the same (baseline 57.3% to 58.3% in week 24).

Resistance to all beta lactam antibiotics in at least 1 isolate was demonstrated in 13% in the AZLI group at baseline which increased to 18.4% at week 24. However, in the TNS group this proportion of subjects decreased from 17% at baseline to 12.3% at week 24.

Resistance to tobramycin increased after exposure to TNS from 29% at baseline to 37% of subjects at week 24, whereas in AZLI-treated subjects without TNS exposure during the trial this proportion with resistance to TNS slightly decreased from 31% at baseline to 27% of subjects at week 24.

These microbiological findings were already reported as a serious risk in previous assessment reports.

The combination of a lack of eradication of PA in lungs of CF patients, with increasing MICs for aztreonam and appearance of cross resistance to bêta-lactam antibiotics after exposure to aztreonam in the resident PA colonies – all more frequent than after treatment with TNS – plus an increase in MRSA isolation in AZLI treated subjects, is of major concern as it may compromise future treatment

options and thus worsen lung function.

These perspectives seriously influence the risk-benefit ratio of AZLI as a treatment option in young AZLI patients and should be included as a warning in the SmPC. RMP needs to be updated.

Supplementary information provided during this procedure

In submitted supplementary information, the MAH re-iterated that AZLI treatment was not associated with a strong decrease in aztreonam susceptibility or the development of cross-resistance to IV beta-lactam antibiotics among paediatric subjects in GS-US-205-0110. Importantly, PA parenteral resistance to aztreonam in paediatric subjects was not predictive of clinical efficacy, an observation that is consistent with previous findings that there is no correlation between *in vitro* PA susceptibility and clinical response to antibiotics in patients with CF. Furthermore, it was argued that AZLI treatment did not lead to the emergence of MRSA in paediatric subjects.

Comment:

Treatment of chronic PA infection in CF requires repeated courses of antibiotics (both inhalational and intravenous) which inherently result in increased MICs of PA to those antibiotics and to selection of other multidrug resistant microorganisms (e.g. Burkholderia, MRSA). Regardless of these issues, considering the increased survival of CF-patients due to administration of antibiotics, this strategy is now mainstay of guidelines.

However, the development of (cross)-resistance progresses differently between various antibiotics and these relative differences were evident in the comparison of AZLI and TNS, although the clinical consequences were not noticed during the period of the study of maximum 48 weeks. Since the resistance-trends in AZLI-treated subjects were unfavorable compared to those treated with TNS, the risk of development of (cross)-resistance in the initial stage of disease negatively influenced the benefit risk ratio of AZLI as a treatment of chronic PA infection in pediatric patients as compared to TNS, because of the life long treatment and decrease in therapeutic options.

1. MIC: various parameters were explored in the total study population as extensively evaluated in the assessment report: a) MIC50 and MIC90 changes in all PA isolates and b) those in the least susceptible PA isolate, and c) increases in the proportion of PA isolates with MIC>8 (= parenteral breakpoint). Different measures, such as geometric MIC in paediatric subjects were not part of the initially presented data.

    a. Ad a): MIC90 increased more than 4 fold after repeated courses of AZLI in some subjects.

    b. Ad b): a 4-fold increase in MIC for aztreonam in the least susceptible PA isolate was reported for 35% of subjects at week 24, whereas in the TNS group only 20% of subjects that were exposed to tobramycin demonstrated a 4-fold increase in MIC for tobramycin.

    c. Ad c): At baseline 39 AZLI-treated patients (34%) had a PA isolate with aztreonam MIC >8 µg/mL and at week 24 in total 56 patients (49%) treated with AZLI had a PA isolate with aztreonam MIC > 8 µg/mL.

As such, these data should be included in the SmPC. Based on these observations a good monitoring of the emergence of PA resistance to aztreonam after AZLI treatment and consequences for the treatment of systemic infections warrants inclusion of appropriate information in section 4.4 and 5.1 of the SmPC in the upcoming Variation application. These sections should contain information on the:

- increase in MIC90 of Aztreonam in PA,

- increase in the proportion of subjects with MIC > 8 (parenteral breakpoint)

after repeated administration of AZLI. The MAH is requested to add these relevant warnings to the SmPC, since repeated determination of susceptibility of PA to administered antibiotics is part of the diagnostic routine in most CF centres. These observations did not influence the increase in FEV1 during the study period, but are clinically relevant.

2. Based on 48 week data, the MAH claims that the decrease in susceptibility to aztreonam of PA does not translate into clinical deterioration *per se*, which has not been evaluated over decades in paediatric patients who require repeated courses of inhalation antibiotics during their life with CF. Furthermore, two other concerns negatively influenced the risk benefit ratio of AZLI in paediatric patients:

    a. Increase in MIC in other bêta-lactam antibiotics was shown in all subjects (adults and children): an increase in PA resistance rates to at least 1 bêta-lactam antibiotic during treatment was demonstrated in AZLI: from baseline (week 0/2) 55.7% to 66.7% in week 24, whereas in TNS this proportion remained the same (baseline 57.3% to 58.3% in week 24). In addition, resistance to all bêta-lactam antibiotics in at least 1 isolate was demonstrated in 13% in the AZLI group at baseline which increased to 18.4% at week 24. However, in the TNS group this proportion of subjects decreased from 17% at baseline to 12.3% at week 24. The now presented data on the subgroup of paediatric patients is not sufficiently powered to diminish the concern based on the overall observations. Consequently,

        - Monitoring of MICs of bêta-lactams should be part of the RMP and be part of the PIP
        - In the SmPC these proportions should be mentioned to inform physicians on possible changes in susceptibility of PA isolates, even though the clinical consequences are not known at this stage

    b. MRSA: more treatment emergent isolation MRSA was reported in the AZLI-treated patients compared to TNS (12% versus 1%). Extension data did not reveal worsening trends. The total number of subjects in GS-US-250-110 with persistent colonization with MRSA was low (n=4). MRSA eradication is only possible with aggressive treatment and rigorous patient segregation and might only then result in clearance in up to 80% of subjects in some CF centers (Doe, J Cyst Fibr, 2010), but no data is provided whether TNS-treated patients were subject to such treatment regimens, although reportedly more anti-*Staphylococcus* concomitant medication usage was used by TNS-treated subjects (9.1%) compared to AZLI-treated subjects (4.4%). This imbalance in use of anti-MRSA drugs is unlikely of influence on the different treatment emergent MRSA isolation rates and should not be incorporated in the SmPC as an explanation of differences in MRSA isolation rates, but the isolation of MRSA should.

        - Monitoring of persistent colonization with MRSA should be part of the RMP

Discussion on clinical safety

No additional AEs or ADRs are observed in study CP-AI-003, CP-AI-005 and CP-AI-007. Although pyrexia show similar frequencies in the adults population, in paediatric patients pyrexia shows higher frequencies (6-12 years: 25% (n=5) and 13-17 years: 16.1%, n=9). Study CP-AI-006 did not show any extra AEs or ADRs.

The reported AEs in study GS-US-205-0110 are in the same order of frequency between paediatric and adults. Cough and reproductive cough most commonly reported. Pyrexia and haemoptysis was reported more frequently in paediatric patients. Pyrexia was reported in children <18 years of age in 46.4% of the AZLI- and 41.9% of the TNS treated groups. Haemoptysis was reported in adolescents aged 13 to 17 years in 21.4% of the AZLI-treated subjects vs 4.3% of the TNS-treated subjects.

Pyrexia is stated in section 4.8 of the SmPC, as "very common".

Based on the review of the safety profile of AZLI in paediatric patients, AZLI appears to be well-tolerated in paediatric patients aged 6 years and older, although exposure was limited. However haemoptysis is of concern especially in children. An increase in frequency has been observed in the long term study GS-US-205-0110. Although the MAH explained that haemoptysis is not an ADR but related to bronchospams, haemoptysis must be included in the RMP as an identified risk. Moreover haemoptysis is to be included in section 4.8 of the SmPC and a warning should be added to section 4.4 preferably with a subsection labeled "**Haemoptysis**".

The CHMP agrees with the MAH that the higher incidence of hospitalization in paediatric patients can be attributed to the severity of CF in children and the prevailing standard of care.

No specific microbiology data with respect to paediatric patients was provided for this variation.

From the long term study GS-US-205-0110, it can be concluded that in the TNS-treated patient group that the MSRA reduced from 20.0% at baseline (week -2) to 10.6% by week 24. In the AZLI-treated group the presence of **MRSA** was 17.4% at baseline (week -2) and remained similar in week 24 (19.8%). However in the extension phase of the same study (where all patients were continued on AZLI) it is shown that the reduction of MRSA remains similar for all patients (AZLI/AZLI and TNS/AZLI). With respect to MSSA it was observed that in the extension phase patients on AZLI/AZLI had same frequencies of MSSA, however an increase in the presence of MSSA was noticed in patients previously on TNS.

Furthermore it is shown that patients treated with AZLI had increasing **PA** from baseline (week -2) 97.0% to 91.3% in week 24. In contrast patients treated with TNS showed a reduction in PA from baseline (week -2) 92.3% to 85.8% in week 24.

Conclusions on clinical safety

Haemoptysis is of concern, especially in children. The RMP and SmPC are updated in this respect.

Differential development of increases in MIC, appearance of cross resistance and possibly persistent colonization with MRSA is evident in the CF patients treated with AZLI compared to TNS. The long term clinical outcomes and differences (i.e., decrease in FEV1 and possible increased need of respiratory hospitalizations) beyond 48 weeks are not known. By adding this information in the SmPC in section 4.4 and 5.1 physicians should be informed about the changes in MICs that can be expected in diagnostic routine. The RMP should contain plans for the observation of these changes and MRSA

isolation rates, including the clinical outcome related to these issues.

2.5. Risk management plan

Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan within this procedure.

Table 29: Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Identified Risks		
Bronchospasm in patients with severe lung disease	Routine pharmacovigilance activities	**Section 4.4 of Cayston SmPC:** *Bronchospasm:* Bronchospasm is a complication associated with nebulised therapies. Patients were pre-treated with a bronchodilator before dosing with study therapy. An acute reduction of ≥ 15% in forced expiratory volume in 1 second (FEV_1) following administration of study therapy was observed in 3% of patients treated with Cayston and 4% of patients receiving placebo despite pre-treatment with a bronchodilator before dosing with study therapy. Patients should use a bronchodilator before each dose of Cayston. If a case of bronchospasm is suspected to be part of an allergic reaction appropriate measures should be taken (see "allergic reactions" paragraph above). **Section 4.8a of Cayston SmPC:** An acute reduction of ≥ 15% in FEV_1 is a complication associated with nebulised therapies, including Cayston (see section 4.4). **Section 4.8b of Cayston SmPC:** *Respiratory, thoracic and mediastinal disorders* Common: bronchospasm **Section 4.8c of Cayston SmPC:** *Bronchospasm* Nebulised therapies, including Cayston, may be associated with bronchospasm (an acute reduction of ≥ 15% in FEV1). In placebo-controlled studies, bronchospasm was observed in 3% of patients treated with Cayston *versus* 4% of patients treated with placebo, despite pre-treatment with a bronchodilator before dosing with study treatment (see

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		section 4.4).
<u>Hemoptysis</u>	**Routine pharmacovigilance activities.** **<u>Review of safety data from 2 PIP studies (GS-US-205-0160, GS-US-205-0162) and a planned study of continuous alternating therapy (CAT) with AZLI and TNS in patients aged 6 years and older with CF and chronic *PA* infection with a primary endpoint of reduction in frequency of pulmonary exacerbations (GS-US-205-0170).</u>**	**Section 4.4 of Cayston SmPC:** ***<u>Haemoptysis</u>*: <u>Inhalation of nebulised solutions may induce a cough reflex. The use of Cayston in paediatric CF patients has been associated with haemoptysis during treatment cycles and could have aggravated underlying conditions. Administration of Cayston in CF patients with active haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.</u>** **Section 4.8b of Cayston SmPC:** ***<u>Respiratory, thoracic and mediastinal disorders</u>*** **<u>Common: haemoptysis</u>**
Important Potential Risks		
Serious hypersensitivity reactions (including erythema multiforme, exfoliative dermatitis, urticaria, rash, petechiae, pruritus, purpura, and pyrexia [with diaphoresis], anaphylaxis and toxic epidermal necrolysis). See also anaphylaxis and toxic epidermal necrolysis below.	Routine pharmacovigilance activities	**Section 4.4 of Cayston SmPC:** Allergic Reactions If an allergic reaction to Cayston does occur, stop administration of the medicinal product and initiate treatment as appropriate. The occurrence of rash may be indicative of an allergic reaction to Cayston. Cross-reactivity may occur in patients with a history of allergy to beta-lactam antibiotics, such as penicillins, cephalosporins, and/or carbapenems. Animal and human data demonstrate low risk of cross-reactivity between aztreonam and beta-lactam antibiotics. Aztreonam, a monobactam, is only weakly immunogenic. Caution is advised when administering Cayston to patients if they have a history of beta-lactam allergy. The following rare and severe adverse reactions, although these have not been observed to date with Cayston, have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis. **Section 4.8b of Cayston SmPC:** *Skin and subcutaneous tissue disorders* Common: rash **Section 4.8c of Cayston SmPC:**

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Allergic Reactions Rash has been reported with the use of Cayston and may be indicative of an allergic reaction to Cayston (see section 4.4). ***Lung function test decreased*** **Lung function test decreased has been reported with use of Cayston, but was not associated with a sustained decrease in FEV1 (see section 5.1).** The following rare and severe adverse reactions, although these have not been observed to date with Cayston, have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.
Anaphylaxis	Routine pharmacovigilance activities	See above for Serious Hypersensitivity Reactions.
Toxic epidermal necrolysis	Routine pharmacovigilance activities	See above for Serious Hypersensitivity Reactions.
Colonization leading to superinfection	Routine pharmacovigilance activities	**Section 4.4 of Cayston SmPC:** The development of antibiotic-resistant *P. aeruginosa* and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled aztreonam therapy could limit treatment options during acute exacerbations. **A decrease in *P. aeruginosa* susceptibility to aztreonam and other beta-lactam antibiotics was observed in clinical studies of Cayston. In a 24-week active-controlled clinical study of Cayston therapy, increases were observed in the MIC_{90} for all *P. aeruginosa* isolates as well as in the percentages of patients with *P. aeruginosa* resistant (MIC above the parenteral breakpoint) to aztreonam, to at least 1 beta-lactam antibiotic, and to all 6 beta-lactam antibiotics tested (see section 5.1). However, decreased *P. aeruginosa* susceptibility was not predictive of clinical efficacy of Cayston during the study.** Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. **The emergence of parenteral *P. aeruginosa***

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		resistance to aztreonam or other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics. An increased prevalence of **methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA),** *Aspergillus* and *Candida* species were observed over time in patients treated with several Cayston treatment courses. **An association between persistent isolation of MRSA and worse clinical outcome has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.** **Section 5.1 of Cayston SmPC:** *Microbiology* In studies of up to six 28-day courses of Cayston therapy, no increases of clinical significance have been observed in the treatment-emergent isolation of other bacterial respiratory pathogens (*Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, and *Staphylococcus aureus*).
Development of resistance (with clinical sequelae) to aztreonam and other antibiotics	Routine pharmacovigilance activities. Prospective observational study linked to US CFF Registry to assess changes in *PA* susceptibility to aztreonam and other antibiotics over a 5-year period (GX-US-205-0128). **Review of safety data from 1 PIP study (GS-US-205-0160) and a planned study of a CAT regimen with AZLI and TNS in patients aged 6 years and older with CF and chronic *PA* infection with a primary endpoint of reduction in frequency of pulmonary exacerbations (GS-US-205-0170).**	**Section 4.4 of Cayston SmPC:** The development of antibiotic-resistant P. aeruginosa and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled aztreonam therapy could limit treatment options during acute exacerbations. **A decrease in P. aeruginosa susceptibility to aztreonam and other beta-lactam antibiotics was observed in clinical studies of Cayston. In a 24-week active-controlled clinical study of Cayston therapy, increases were observed in the MIC_{90} for all P. aeruginosa isolates as well as in the percentages of patients with P. aeruginosa resistant (MIC above the parenteral breakpoint) to aztreonam, to at least 1 beta-lactam antibiotic, and to all 6 beta-lactam antibiotics tested (see section 5.1). However, decreased P. aeruginosa susceptibility was not predictive of clinical efficacy of Cayston during the study.** Among patients with multidrug-

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. **The emergence of parenteral *P. aeruginosa* resistance to aztreonam or other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics.** **An increased prevalence of methicillin-resistant Staphylococcus aureus (MRSA), methicillin-sensitive S. aureus (MSSA), Aspergillus and Candida species was observed over time in patients treated with several Cayston treatment courses. An association between persistent isolation of MRSA and worse clinical outcome has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.** **Section 5.1 of Cayston SmPC:** Mechanisms of resistance Loss of susceptibility to aztreonam in CF patients with *P. aeruginosa* occurs either through selection of strains with mutations located on the chromosome or rarely through acquisition of plasmid/integrin mediated genes. Known mechanisms of resistance to aztreonam mediated by mutation of chromosomal genes include: hyperexpression of the Class C beta-lactamase AmpC and up-regulation of the efflux pump MexAB OprM. The known mechanism of resistance to aztreonam mediated by acquisition of genes involves acquisition of extended spectrum beta-lactam enzymes (ESBLs) that hydrolyse the four-member, nitrogen-containing ring of aztreonam. ESBLs from Class A, B and D beta-lactamases generally have little or no activity against aztreonam. Class A beta-lactamases reported to hydrolyse aztreonam include the VEB type (primarily Southeast Asia), PER type (Turkey), and GES and IBC types (France, Greece, and S. Africa). There are rare reports of organisms with metallo-beta-lactamases (MBLs), Class B, that are resistant to aztreonam, VIM 5 (*K. pneumoniae* and *P. aeruginosa* -

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		Turkey), VIM 6 (*P. putida* - Singapore) and VIM 7 (*P. aeruginosa* - United States), however, it is possible that these organisms were expressing multiple resistance mechanisms and thus a MBL was not responsible for the observed resistance to aztreonam. There are rare reports of Class D beta-lactamases from clinical isolates of *P. aeruginosa*, OXA 11 (Turkey) and OXA 45 (United States) that hydrolyse aztreonam. Microbiology A single sputum sample from a CF patient may contain multiple isolates of *P. aeruginosa* and each isolate may have a different level of *in vitro* susceptibility to aztreonam. The *in vitro* antimicrobial susceptibility test methods used for parenteral aztreonam therapy can be used to monitor the susceptibility of *P. aeruginosa* isolated from CF patients. In the Phase 3 placebo-controlled studies of Cayston, local aztreonam concentrations generally exceeded aztreonam MIC values for *P. aeruginosa*, regardless of the level of *P. aeruginosa* susceptibility. Treatment with **up to nine** 28 day courses of 75 mg 3 times a day Cayston therapy resulted in clinically important improvements in respiratory symptoms, pulmonary function, and sputum *P. aeruginosa* CFU density; **no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed, whereas MIC_{90} increased intermittently to 4 times the initial MIC. In a 24-week active-controlled study of Cayston therapy, no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed, whereas MIC_{90} increased to 4 times the initial MIC. At the end of the study, the percentage of patients with aztreonam MIC for *P. aeruginosa* above the parenteral breakpoint (> 8 µg/ml) increased from 34% at baseline to 49%, the percentage of patients with *P. aeruginosa* resistant to at least 1 beta-lactam antibiotic increased from 56% at baseline to 67%, and the percentage of patients with *P. aeruginosa* resistant to all 6 beta-lactam antibiotics tested increased from 13% at baseline to 18%. There is a risk that *P. aeruginosa* isolates may develop**

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		resistance to aztreonam or other beta-lactam antibiotics in patients treated with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam and other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics. However, similar improvements in lung function were seen after treatment with Cayston among patients with aztreonam susceptible or resistant *P. aeruginosa* isolates. **In studies of up to nine 28-day courses of Cayston therapy, no increases of clinical significance were observed in the treatment-emergent isolation of other gram-negative bacterial respiratory pathogens (*Burkholderia* species, *Stenotrophomonas maltophilia* and *Alcaligenes* species). During the 6-month randomised phase of Study GS-US-205-0110, treatment-emergent isolation of MSSA and MRSA was observed more commonly among Cayston-treated patients than Tobramycin Nebuliser Solution (TNS)-treated patients. The majority of the treatment- emergent isolations were intermittent. Treatment-emergent persistent isolation (defined as absent at screening/baseline then present at 3 or more subsequent consecutive visits) of MSSA occurred in 6% of Cayston-treated patients compared to 3% of TNS-treated patients. Treatment-emergent persistent isolation of MRSA occurred in 3% of Cayston-treated patients compared to no TNS-treated patients. An association between persistent isolation of MRSA and more severe disease and increased mortality has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.**

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Off-label use in pediatric patients (under 6 years of age)	Routine pharmacovigilance activities	**Section 4.1 of Cayston SmPC:** Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older. **Section 4.2 of Cayston SmPC:** *Paediatric population* **Cayston is indicated in children aged 6 years and older. In clinical studies with Cayston patients younger than 6 years of age were excluded. The safety and efficacy of Cayston in children younger than 6 years of age has not been established. The dosing in children aged 6 years and older is the same as for adults. Dosage is not based on weight or adjusted for age.** **Section 5.1 of Cayston SmPC:** *Paediatric population* **A total of 137 paediatric patients aged 6 to 17 years with FEV1 ≤ 75% predicted have receive Cayston in Phase 2 and Phase 3 clinical studies. Paediatric patients had clinical improvements with Cayston as determined by an increase in FEV_1, improvement in CFQ-R respiratory symptoms scores and decline in *P. aeruginosa* sputum density. Cayston is indicated for use in paediatric patients aged 6 years and older based on the above clinical experience.** The European Medicines Agency has deferred the obligation to submit the results of studies with Cayston in one or more subsets of the paediatric population in cystic fibrosis patients with *Pseudomonas aeruginosa* pulmonary infection/colonisation (see section 4.2 for information on paediatric use).

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Missing Information		
Safety data in adults (including long-term safety)	Routine pharmacovigilance activities. Review of safety data from expanded access program EA-US-205-0122, a planned clinical study comparing AZLI BID and TID (GS-US-205-0163), **and a planned study of a CAT regimen with AZLI and TNS (GS-US-205-0170).** Monitor safety data from study GX-US-205-0128 for CF patients aged 18 years and older with chronic *PA*	Update of labeling as appropriate.
Safety data in children (including long-term safety)	Routine pharmacovigilance activities Review of safety data from expanded access program EA-US-205-0122, 3 PIP studies (GS-US-205-0162, GS-US-205-XXX2, GS-US-205-0160), a planned clinical study comparing AZLI BID and TID (GS-US-205-0163), **and a planned study of a CAT regimen with AZLI and TNS (GS-US-205-0170).** Monitor safety data from study GX-US-205-0128 for an 18-month minimum for each CF patient aged 6 to less than 18 years with chronic *PA* infection/colonization.	Updating of labeling as appropriate.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.6. Changes to the Product Information

The MAH proposed changes to the Product Information (PI). Following review, the following changes to SmPC were agreed by the CHMP:

4.1 Therapeutic indications

Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Patients should use a bronchodilator before each dose of Cayston. Short acting bronchodilators can be taken between 15 minutes and 4 hours and long acting bronchodilators can be taken between 30 minutes and 12 hours prior to each dose of Cayston.

For patients taking multiple inhaled therapies, the recommended order of administration is as follows:

1. bronchodilator
2. mucolytics
3. and lastly, Cayston.

Adults

The recommended dose for adults is 75 mg three times per 24 hours for 28 days.

Doses should be taken at least 4 hours apart.

Cayston may be taken in repeated cycles of 28 days on therapy followed by 28 days off Cayston therapy.

Paediatric population

Cayston is indicated in children aged 6 years and older. In clinical studies with Cayston patients younger than 6 years of age were excluded. The safety and efficacy of Cayston in children younger than 6 years of age has not been established. The dosing in children aged 6 years and older is the same as for adults. Dosage is not based on weight or adjusted for age.

4.4 Special warnings and precautions for use

[…]

The following rare and severe adverse reactions have not been observed to date with Cayston, but have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

Bronchospasm

Bronchospasm is a complication associated with nebulised therapies. Patients were pre-treated with a bronchodilator before dosing with study therapy. In placebo-controlled studies, an acute reduction of ≥ 15% in forced expiratory volume in 1 second (FEV_1) following administration of study therapy was observed in 3% of patients treated with Cayston and 4% of patients receiving placebo despite pre-treatment with a bronchodilator before dosing with study therapy. Patients should use a bronchodilator before each dose of Cayston. If a case of bronchospasm is suspected to be part of an allergic reaction appropriate measures should be taken (see "allergic reactions" paragraph above).

Other precautions

Efficacy has not been established in patients with FEV_1 > 75% predicted. Patients with *Burkholderia cepacia* isolated from sputum within the previous 2 years were excluded from the clinical studies.

Aztreonam for injection must not be used in the Altera or other nebulisers. Aztreonam for injection has not been formulated for inhalation, and contains arginine, a substance known to cause pulmonary inflammation.

Resistance to aztreonam, other antibiotics and treatment-emergent microorganisms

The development of antibiotic-resistant *P. aeruginosa* and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled aztreonam therapy could limit treatment options during acute exacerbations. A decrease in *P. aeruginosa* susceptibility to aztreonam and other beta-lactam antibiotics was observed in clinical studies of Cayston. In a 24-week active-controlled clinical study of Cayston therapy, increases were observed in the MIC_{90} for all *P. aeruginosa* isolates as well as in the percentages of patients with *P. aeruginosa* resistant (MIC above the parenteral breakpoint) to aztreonam, to at least 1 beta-lactam antibiotic, and to all 6 beta-lactam antibiotics tested (see section 5.1). However, decreased *P. aeruginosa* susceptibility was not predictive of clinical efficacy of Cayston during the study. Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam or other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics.

An increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *S. aureus* (MSSA), *Aspergillus* and *Candida* species was observed over time in patients treated with several Cayston treatment courses. An association between persistent isolation of MRSA and worse clinical outcome has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.

4.8 Undesirable effects

a. Summary of the safety profile

Assessment of adverse reactions is based on experience in four Phase 3 clinical studies involving CF patients (n = 539) and post-marketing spontaneous reporting. In two Phase 3 placebo-controlled studies patients received Cayston 75 mg 2 times (69 patients) or 3 times a day (146 patients) for 28 days. In one Phase 3 open-label follow-on study 274 patients received up to nine 28-day treatment courses of Cayston 75 mg 2 times or 3 times a day. In one Phase 3 active-controlled study, 136 patients received up to three 28-day courses of Cayston 75 mg 3 times a day during the randomised phase; an additional 65 patients received up to three 28-day courses in an open-label extension phase.

c. Description of selected adverse reactions

[…]

The following rare and severe adverse reactions have not been observed to date with Cayston, but have been reported after parenteral use of other aztreonam containing products: toxic epidermal necrolysis, anaphylaxis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.

d. Paediatric population

A total of 137 paediatric patients aged 6 to 17 years with $FEV_1 \leq 75\%$ predicted have received Cayston in Phase 2 and Phase 3 clinical studies (6-12 years, n = 35; 13-17 years, n = 102).

In Phase 2 and Phase 3 placebo-controlled clinical studies of Cayston, pyrexia was observed at a higher incidence rate in paediatric patients aged 6 to 17 years (18%) compared to adults (8%).

5.1 Pharmacodynamic properties

[…]

Mechanisms of resistance

[…]

ESBLs from Class A, B and D beta-lactamases may have activity against aztreonam. Class A beta-lactamases reported to hydrolyse aztreonam include the VEB type (primarily Southeast Asia), PER type

(Turkey), and GES and IBC types (France, Greece, and S. Africa). There are rare reports of organisms with metallo-beta-lactamases (MBLs), Class B, that are resistant to aztreonam, VIM-5 (*K. pneumoniae* and *P. aeruginosa* - Turkey), VIM-6 (*P. putida* - Singapore) and VIM-7 (*P. aeruginosa* - United States), however, it is possible that these organisms were expressing multiple resistance mechanisms and thus a MBL was not responsible for the observed resistance to aztreonam. There are rare reports of Class D beta-lactamases from clinical isolates of *P. aeruginosa*, OXA-11 (Turkey) and OXA-45 (United States) that hydrolyse aztreonam.

Microbiology

[…]

Treatment with up to nine 28-day courses of 75 mg 3 times a day Cayston therapy resulted in clinically important improvements in respiratory symptoms, pulmonary function, and sputum *P. aeruginosa* CFU density; no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed, whereas MIC_{90} increased intermittently to 4 times the initial MIC. In a 24-week active-controlled study of Cayston therapy, no increases in *P. aeruginosa* MIC_{50} (± 2 dilution change) were observed, whereas MIC_{90} increased to 4 times the initial MIC. At the end of the study, the percentage of patients with aztreonam MIC for *P. aeruginosa* above the parenteral breakpoint (> 8 µg/ml) increased from 34% at baseline to 49%, the percentage of patients with *P. aeruginosa* resistant to at least 1 beta-lactam antibiotic increased from 56% at baseline to 67%, and the percentage of patients with *P. aeruginosa* resistant to all 6 beta-lactam antibiotics tested increased from 13% at baseline to 18%. There is a risk that *P. aeruginosa* isolates may develop resistance to aztreonam or other beta-lactam antibiotics in patients treated with Cayston. The emergence of parenteral *P. aeruginosa* resistance to aztreonam and other beta-lactam antibiotics may have potential consequences for the treatment of acute pulmonary exacerbations with systemic antibiotics. However, similar improvements in lung function were seen after treatment with Cayston among patients with aztreonam susceptible or resistant *P. aeruginosa* isolates.

In studies of up to nine 28-day courses of Cayston therapy, no increases of clinical significance were observed in the treatment-emergent isolation of other gram-negative bacterial respiratory pathogens (*Burkholderia* species, *Stenotrophomonas maltophilia and Alcaligenes* species). During the 6-month randomised phase of study GS-US-205-0110, treatment-emergent isolation of MSSA and MRSA was observed more commonly among Cayston-treated patients than Tobramycin Nebuliser Solution (TNS)-treated patients. The majority of the treatment-emergent isolations were intermittent. Treatment-emergent persistent isolation (defined as absent at screening/baseline then present at 3 or more subsequent consecutive visits) of MSSA occurred in 6% of Cayston-treated patients compared to 3% of TNS-treated patients. Treatment-emergent intermittent isolation of MRSA occurred in 7% of Cayston-treated patients compared to 1% of TNS-treated patients and treatment-emergent persistent isolation of MRSA occurred in 3% of Cayston-treated patients compared to no TNS-treated patients. An association between persistent isolation of MRSA and more severe disease and increased mortality has been reported in the literature. During clinical studies of Cayston, isolation of MRSA did not result in worsening of lung function.

Clinical efficacy and safety

Cayston was compared to TNS over three 28-day courses of treatment in a randomised, active-controlled, multicenter study (GS-US-205-0110). Patients participating in this study in Europe who completed at least 1 course of Cayston or TNS during the randomised phase could subsequently receive up to three 28-day courses of Cayston in an open-label extension phase. Entry criteria included CF, $FEV_1 \leq 75\%$ predicted, stable pulmonary disease, a recent positive sputum culture for *P. aeruginosa*, and previous treatment with aerosolised antibiotics without demonstration of drug intolerance.

Cayston was evaluated over a period of 28-days of treatment (one course) in two randomised, double-blind, placebo-controlled, multicentre studies (CP-AI-005 and CP-AI-007). Patients participating in these studies could subsequently receive multiple courses of Cayston in an open-label follow-on study (CP-AI-006). Entry criteria included CF, baseline FEV_1 between 25% and 75% predicted, and chronic *P. aeruginosa* lung infection.

Overall, 539 patients (78% adults) were treated in these studies. Studies were conducted using the Altera Nebuliser System to administer Cayston.

GS-US-205-0110

In GS-US-205-0110, 268 patients with CF and chronic *P. aeruginosa* lung infection were randomised and received Cayston (n = 136) or TNS (n = 132). Fifty-nine paediatric patients aged 6 to 17 years were included in the study.

Patients were randomised in a 1:1 ratio to receive either Cayston (75 mg) administered by inhalation 3 times a day or TNS (300 mg) administered 2 times a day. Treatments were administered for three cycles of 28 days on therapy followed by 28 days off therapy. The co-primary endpoints were non-inferiority of Cayston to TNS in relative change from baseline to Day 28 in FEV_1 % predicted and superiority of Cayston to TNS in actual change from baseline in FEV_1 % predicted across 3 treatment courses (the average of the actual change in FEV_1 % predicted observed at the end of each treatment course).

The adjusted mean percent change from baseline to Day 28 in FEV_1 % predicted was 8.35 and 0.55 in the Cayston and TNS groups, respectively (treatment difference: 7.80; p = 0.0001; 95% CI: 3.86, 11.73). The adjusted mean actual change from baseline in FEV_1 % predicted across 3 treatment courses was 2.05 and -0.66 in the Cayston and TNS groups, respectively (treatment difference: 2.70; p = 0.0023; 95% CI: 0.98, 4.43). Patients treated with Cayston experienced a longer time to need for i.v. antipseudomonal antibiotics related to respiratory events compared to TNS-treated patients (p = 0.0025). The Kaplan-Meier estimates for this event rate at week 24 were 36% in Cayston-treated patients and 54% in TNS-treated patients. Additionally, Cayston-treated patients had fewer hospitalisations due to respiratory events (40 *versus* 58, p = 0.044) and fewer respiratory events requiring the use of i.v. or inhaled antipseudomonal antibiotics (84 *versus* 121, p = 0.004) than TNS-treated patients. Cayston-treated patients also demonstrated larger mean improvements in CFQ-R respiratory symptoms scores compared to TNS-treated patients across 3 treatment courses (6.30 *versus* 2.17, p = 0.019).

In the limited subgroup of patients who received inhaled tobramycin for less than 84 days in the previous 12 months (n = 40), lung function improvements at Day 28 and across three 28-day treatment courses were numerically smaller among Cayston-treated patients than TNS-treated patients.

[…]

CP-AI-006

[…]

Over nine 28-day courses of therapy, measures of pulmonary function (FEV_1), CFQ-R respiratory symptoms scores, and *P. aeruginosa* sputum density showed a trend to improvement while the patients were on treatment compared with off treatment.

[…]

Paediatric population

A total of 137 paediatric patients aged 6 to 17 years with $FEV_1 \leq 75\%$ predicted have received Cayston in Phase 2 and Phase 3 clinical studies. Paediatric patients had clinical improvements with Cayston as determined by an increase in FEV_1, improvement in CFQ-R respiratory symptoms scores and decline in *P. aeruginosa* sputum density. Cayston is indicated for use in paediatric patients aged 6 years and older based on the above clinical experience.

5.2 Pharmacokinetic properties

[…]

Paediatric population

The Phase 2 and 3 placebo-controlled, registrational studies permitted comparison of plasma concentrations 1 hour post dose of Cayston by age (6 to 12 years, 13 to 17 years, and ≥ 18 years). Data from these studies revealed minimal differences in mean plasma aztreonam concentrations between age groups in patients receiving Cayston 75 mg 3 times a day.

Pooled sputum concentration data from the Phase 2 and 3 registrational studies revealed some evidence of lower mean sputum concentrations in patients aged 13 to 17 years following one dose of Cayston 75 mg 3 times a day. However, all mean sputum concentration values were associated with relatively large standard deviations.

5.3 Preclinical safety data

[…]

Fertility, teratology, perinatal and postnatal studies were conducted with aztreonam for i.v. injection in rats at daily doses up to 750 mg/kg without adverse effects.

During the procedure, the CHMP requested further amendments to the PI as discussed in detail above. The following additional amendments to the Product Information have been agreed:

4.4 Special warnings and precautions for use

[…]

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex. The use of Cayston in paediatric CF patients has been associated with haemoptysis during treatment cycles and could have aggravated underlying conditions. Administration of Cayston in CF patients with active haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

4.8 Undesirable effects

[…]

b. Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment from clinical study and post-marketing experience are listed below by body system organ class and frequency.

Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

Respiratory, thoracic and mediastinal disorders:	
Very common:	cough, nasal congestion, wheezing, pharyngolaryngeal pain, dyspnoea
Common:	bronchospasm[1], chest discomfort, rhinorrhoea, haemoptysis[1]
Skin and subcutaneous tissue disorders:	
Common:	rash[1]
Musculoskeletal and connective tissue disorders	
Common:	arthralgia
Uncommon:	joint swelling
General disorders and administration site conditions:	
Very common:	pyrexia
Investigations	
Common:	lung function test decreased[1]

[1] See section c. Description of selected adverse reactions

c. Description of selected adverse reactions

Bronchospasm

Nebulised therapies, including Cayston, may be associated with bronchospasm (an acute reduction of ≥ 15% in FEV_1). In placebo-controlled studies, bronchospasm was observed in 3% of patients treated with Cayston *versus* 4% of patients treated with placebo, despite pre-treatment with a bronchodilator before dosing with study treatment (see section 4.4).

Haemoptysis

Inhalation of nebulised solutions may induce a cough reflex which could aggravate underlying

conditions (see section 4.4).

Allergic reactions

Rash has been reported with the use of Cayston and may be indicative of an allergic reaction to Cayston (see section 4.4).

Lung function test decreased

Lung function test decreased has been reported with use of Cayston, but was not associated with a sustained decrease in FEV_1 (see section 5.1).

Changes were also made to the PL to bring it in line with the amended SmPC.

2.7. Significance of paediatric studies

The obligation to submit the results of studies with Cayston in one or more subsets of the paediatric population in cystic fibrosis patients with *Pseudomonas aeruginosa* pulmonary infection/colonisation has been deferred.

3. Overall conclusion and impact on the benefit/risk balance

Cayston (Aztreonam lysine) 75 mg TID (AZLI) has been approved for adult patients with Cystic Fibrosis for the suppressive therapy of chronic *Pseudomonas aeruginosa* (PA) infection. The current variation concerns the extension of use of AZLI to children and adolescents.

Benefits

Beneficial effects

Conservation of lung function in children and adolescents was demonstrated in GS-US-205-0110 that was in line with the non-inferiority results in adults compared to TNS. These effects translated into favourable CFQ-R RSS scores in paediatric patients and hospitalization rates similar to TNS. The MAH has demonstrated that these data were applicable to all subgroups including children and adolescents, including patients with increased MIC to aztreonam during the period of observation. Also, in the 24 week extension phase after the randomisation phase, lung function as measured by FEV_1 (expected) was maintained after administration of each cycle of AZLI during one month.

As such, Cayston has demonstrated non-inferiority to Tobramycin inhalation for the same indication: "suppressive therapy of chronic PA infection".

Risks

Unfavourable effects

Repeated rounds of administration of AZLI resulted in the total group (adults and children) in an increase in MIC_{90} to aztreonam in some individuals, an increase in proportions of patients with PA with MIC to aztreonam above the parenteral breakpoint (>8 µg/ml), an increase in numbers of PA isolates with cross-resistance to betalactam antibiotics, treatment-emerging isolation of MRSA, occurrence of

haemoptysis and direct post-treatment decrease of lung function test

Uncertainty in the knowledge about the unfavourable effects

MIC to aztreonam: Also in the pivotal trial of tobramycin inhalation in CF patients (Ramsey, NEJM, 1999), a trend towards an increase in the MIC of tobramycin in the PA isolates from the patients receiving tobramycin but not in the isolates from the patients receiving placebo was observed. Therefore, these findings are not unexpected. However, although an increase in the MIC90 to aztreonam was measured, FEV1 changes were not reversed in these subjects when AZLI was administered during the study period. Long term consequences due to acquisition of PA isolates with increased MIC to aztreonam associated with inhalation of AZLI in young CF patients are unknown, but unfavourable effects might be overcome by alternating antibiotic classes.

Beta lactam cross resistance: the trends as reported for the total group (adults and children) are related to extensive pre-exposure to antibiotics or healthcare associated transmission. Subgroup analysis in paediatric patients did not reveal these trends, because of very small numbers and because pre-study exposure to antibiotics is more limited than in adult CF patients. Long term consequences (i.e., decrease of therapeutic options in case of exacerbations) due to acquisition of PA isolates with increased MIC to bêta-lactam antibiotics associated with inhalation of AZLI in young CF patients are yet unknown.

MRSA: most treatment-emergent isolation of MRSA was temporary in the total study population, but trends appeared unfavourable in the AZLI-arm. Whether this effect was related to MRSA-suppressive therapy with tobramycin in the comparator arm or due to other anti-MRSA medication or healthcare associated acquisition is unknown.

Haemoptysis: in the clinical manifestations of CF, haemoptysis is a common symptom due to damaged airways, but causes can be multiple and are not necessarily associated with cough reflex provoked by inhalational antibiotics. The latter factor could have contributed to some of the 12 episodes of haemoptysis in the paediatric AZLI-arm in 8 on-treatment episodes, but the MAH attributes other factors to these occurrences, since in placebo-controlled studies an increased incidence of haemoptysis was not noticed in the AZLI-arm.

Lung function test decreased: during repeated cycles of administration a substantial proportion (40%) had an immediate post-treatment decreased lung function, which did not negatively influence the FEV_1 endpoint. This effect is a known temporary consequence of inhalation antibiotics, but clinical consequences (e.g. haemoptysis) are unknown. Regardless of this AE in a substantial proportion of subjects, the TID administration of AZLI compared to BID TNS apparently didn't result in lower patient satisfaction as measured by CFQ-R RSS score.

Balance

The conservation of lung function in young CF patients due to AZLI was evident in the comparison with TNS, whereas the observed negative clinical consequences of MIC changes are yet unknown. Concerning the two AEs (haemoptysis, lung function test decreased), the issue is not whether AZLI is associated with an *increased* frequency of these symptoms compared to other agents or placebo, but at least the reported association in CF patients should be mentioned in the SmPC.

Benefit-risk balance

Since the benefits of adding an additional inhalational antibiotic of a different class to the therapeutic

arsenal in the treatment of chronic PA infection in CF patients have been established and antibiotic therapy courses of different classes may be alternated, the observed risks may be limited. The observations of MIC changes and haemoptysis/decreased lung function test are included in the SmPC (sections 4.4 and 4.8 respectively).

Discussion on the benefit-risk assessment

The benefit risk is considered positive. Regardless of a potential negative effect of observed microbiological trends, FEV_1 function was maintained or showed favourable results during at least 48 weeks. Whether these trends, observed in the total population (adults and children) in the comparative study of AZLI versus TNS, might compromise future treatment strategies of chronic PA infection in paediatric CF patients is yet unknown. Likely developments will include alternating treatment regimens using various antibiotics for the treatment of chronic PA infection in CF. Since various classes are now approved, (temporary) class-resistance might be counteracted by switching between classes if tolerated by patients. As one of the treatment options, AZLI can decrease the decline of lung function deterioration in CF resulting from chronic PA infection and has shown to delay hospitalization due to respiratory events.

Long term data of the influence of the trends in increase of MIC of aztreonam and bêta-lactams on both hospitalization rates or lung function deterioration will be collected as outlined in the RMP, since the long term consequences in the young population of CF patients are yet unknown. The MAH is requested to specifically monitor these issues in the approved PIP-studies as well. Since MRSA was mostly intermittently isolated and permanent isolation was rather rare, at least monitoring of MRSA isolation rates in the PIP-studies, in larger groups and during longer periods is required.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC in order to include paediatric patients aged 6 years and older, to include long-term, repeated use data and specifically to reflect clinical treatment outcomes.

The Package Leaflet was proposed to be updated in accordance.

The requested variation proposes amendments to the Update of Summary of Product Characteristics, and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the medicinal product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA