Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cayston

aztreonam

Procedure No.: EMEA/H/C/000996/R/0015

Note

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

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London, 23 June 2011
EMA/CHMP/370905/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on the renewal of the conditional marketing authorisation for Cayston

International non-proprietary name: **aztreonam**

Procedure No.: **EMA/H/C/000996/R/15**

Marketing Authorisation Holder (MAH): **Gilead Sciences International Ltd.**

1. Background information on the renewal

1.1. Conditional Marketing Authorisation

On 21 September 2009, the European Commission issued a conditional Marketing Authorisation (MA) for Cayston based on a positive Opinion adopted by the CHMP on 25 June 2009. This implied that, pursuant to Regulation (EC) No 507/2006, the Marketing Authorisation Holder (MAH) had to complete ongoing studies, or to conduct new studies, as listed in Annex II.C of the MA, the so-called Specific Obligations (SOs). These data form the basis of the renewal of the conditional MA.

On 26 August 2010 the European Commission issued a Decision on the first Renewal of the Conditional Marketing Authorisation, following a positive CHMP Opinion on 24 June 2010.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH.

Therefore, the Marketing Authorisation Holder Gilead Sciences International Ltd. submitted to the EMA on 16 March 2011 an application for the second renewal of the conditional MA for Cayston, which expires on 22 September 2011.

1.2. Steps taken during the renewal of the conditional MA assessment procedure

The Marketing Authorisation Holder submitted an application for renewal of the Conditional Marketing Authorisation on: 16 March 2011

The procedure started on: 20 March 2011

The Rapporteur's assessment report was circulated to all CHMP Members on: 27 April 2011

The Rapporteur's updated assessment report was circulated to all CHMP Members on: 17 June 2011

The CHMP, during its June 2011 plenary meeting, issued a positive Opinion on the switching of the Conditional Marketing Authorisation to a full one.

2. Background information on the medicinal product

The present submission pertains to the second (annual) renewal application of the conditional marketing authorisation for Cayston 75 mg, powder and solvent for nebuliser solution. The CHMP issued a final positive Opinion for granting a conditional MA to Cayston on 25 June 2009. The conditional marketing authorisation was renewed on 26 August 2010.

The expiry date of the current authorisation is 22 September 2011.

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

The product is currently marketed 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 1 August 2011: Luxembourg and The Netherlands
- from 1 September 2011: Spain

Currently approved indication(s): Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* 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.

Inspection

On 28 September 2010, Gilead informed the European Medicines Agency of receipt of a Warning Letter from the FDA subsequent to a GMP inspection conducted at Gilead's manufacturing facility located at 650 Cliffside Drive in San Dimas, California from 25 January to 12 February 2010. Gilead stated that the room under consideration is not used for the manufacture of Cayston. Gilead also confirms that the aseptic processing areas for Cayston met and continue to meet ISO 5 conditions.

PIP submissions

EMEA-000827-PIP01-09 (completed)

On 29 October 2010 the decision of an agreed PIP was issued by the EMA.

Indications targeted by the PIP:

1. Treatment of initial *Pseudomonas aeroginosa* pulmonary infection/colonisation in patients with cystic fybrosis.
2. Treatment of chronic *Pseudomonas aeroginosa* pulmonary infection/colonisation in patients with cystic fybrosis.

Subsets of the paediatric population from 3 months to less than 18 years of age

EMEA-000827-PIP01-09-MO1 (completed)

On 20 May 2011 the modification of an agreed PIP was issued by the EMA. The modification pertained the amendment of timelines as outlined in the initial PIP.

Hence the MAH requested a partial compliance check on 24 May 2011 in order to prepare a type II variation.

EMEA-000827-PIP02-10

The MAH submitted (14 February 2011) a second PIP (EMEA-000827-PIP02-10) for a new indication: treatment of Burkholderia infection in patients with CF.

This application was however withdrawn on 05 May 2011.

3. Scientific data provided by the MAH since the granting of the conditional MA

3.1. List of all Specific Obligations (SOs) and Follow-up measures (FUMs) submitted since the granting of the conditional MA

Since granting the conditional MA the MAH has submitted the following SOs and FUMs:

Specific Obligations

Area	SO Number and Description as described in Letter of Undertaking dated 24 June 2009.	Due Date	Date Submitted	Regulatory Status	Date when Resolved
Clinical	**SO1** (SIAMED PAC No.SOB7): The applicant commits to submit the results of study GS-US-205-0110 and other available long term data.	September 2010	Long term data from Study GS-US-205-0110 submitted on 29 September 2010	First assessment report adopted on 16 December 2010. Follow-up assessment concluded simultaneous to this report	23 June 2011 EMA/6202/2012
		July 2010	Long-term data from study CP-AI-006 submitted 19 March 2010	Fulfilled	26 August 2010 (As part of the European Commission Decision for the 2010 Annual Renewal application). EMA/CHMP/372203/2010
	SO2 (SIAMED PAC No.SOB8): Ongoing studies (ages 6 years and older): Study GS-US-205-0110: Open-label, randomized Phase 3 study to evaluate the efficacy and safety of Cayston versus Tobramycin Nebulizer Solutions (TNS) in an intermittent aerosolized regimen in patients with CF.	September 2010	29 September 2010	First assessment report adopted on 16 December 2010. Follow-up assessment concluded simultaneous to this report	23 June 2011 EMA/6202/2012

Area	SO Number and Description as described in Letter of Undertaking dated 24 June 2009.	Due Date	Date Submitted	Regulatory Status	Date when Resolved
	SO2 (SIAMED PAC No.SOB9): Ongoing studies (ages 6 years and older): Study GS-US-205-0117: Phase 3, double-blind, multi-center, multinational randomized, placebo-controlled trial evaluating AZLI in patients with cystic fibrosis, mild lung disease, and PA. The final clinical study report will be available by December 2009	December 2009	22 December 2009	Fulfilled	18 March 2010 EMA/CHMP/189204/2010
	SO2 (SIAMED PAC No.SOB10): A review of all paediatric data from controlled studies will be provided by September 2010.	September 2010	29 September 2010	Fulfilled	29 September 2010
	SO2 (SIAMED PAC No.SOB11): The applicant commits to a paediatric development of the product consisting of well controlled trials to support short-term and long-term repeated use in this patient group.	March 2010	PIP application submitted to the PDCO on 08 March 2010	Fulfilled	PIP application approved 29 October 2010 PIP No: EMEA 000827-PIP-01-09 P/228/2010

Quality related FUMs

Area	FUM Number and Description as described in Letter of Undertaking dated 24 June 2009	Due Date	Date Submitted	Regulatory Status	Date when Resolved and EMA Fax Ref number
Quality *Drug Substance*	**FUM 1** (SIAMED PAC No.FUM1): The applicant undertakes to prepare samples of the cis-AZTH-2 and cis-aztreonam and demonstrate that they are not present as impurities in aztreonam.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
	FUM 2 (SIAMED PAC No.FUM1): Gilead Sciences will continue to work with the supplier of aztreonam drug substance, to produce development data that confirms removal of reagents from the synthesis, and to provide the data to demonstrate appropriate selectivity of the residual solvent method TM-101.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
	FUM 3 (SIAMED PAC No.FUM1): Confirmation that stability studies using the proposed new Hicoflex bag will be performed.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010

Area	FUM Number and Description as described in Letter of Undertaking dated 24 June 2009	Due Date	Date Submitted	Regulatory Status	Date when Resolved and EMA Fax Ref number
	FUM 4 (SIAMED PAC No.FUM1): An in vitro mammalian cell gene mutation test, (the HPRT mutation test according to the OECD guideline 476) will be performed and submitted. In addition to the audited draft reports for the remaining genotoxicity studies on drug substance and drug product, the applicant will also submit the DEREK structural analysis currently being performed	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/48709/2010
Quality *Drug Product*	**FUM 7** (SIAMED PAC No.FUM1): The used method for gel electrophoresis of lysine monohydrate will be described. The method will be validated with respect to the smallest peptide detectable. The smallest peptide of the molecular weight standards has been 10 kDa. It will be validated that small peptides above 2000 Da can be detected and stained.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
	FUM 8 (SIAMED PAC No.FUM1): The applicant will present the appropriate validation data as a FUM to demonstrate that TM-097 will detect and resolve impurities GS-9399, GS-9394 and GS-9395.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
	FUM 9 (SIAMED PAC No.FUM1): Although validated, the assay method for the stability samples appears to be quite variable and the exact reason is unclear. The applicant will commit to reviewing this method and improving its accuracy or sample preparation as required.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
	FUM 10 (SIAMED PAC No.FUM1): The color of the solution will be specified by comparison with a standard solution according to Ph. Eur. 2.2.2.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
Quality *Solvent*	**FUM 11** (SIAMED PAC No.FUM1): The requested bioburden limit of NMT 10 CFU/100 ml has been adopted for the solvent, the applicant will agree to control the microbiological quality of the excipients used for the solvent manufacture.	30 October 2009	30 October 2009	Fulfilled	21 January 2010 EMA/CHMP/38549/2010
	FUM 19 (SIAMED PAC No.FUM26):	31 May 2010	25 May 2010	Fulfilled	12 August 2010

Area	FUM Number and Description as described in Letter of Undertaking dated 24 June 2009	Due Date	Date Submitted	Regulatory Status	Date when Resolved and EMA Fax Ref number
	Resultant of variation EMEA/H/C/996/II/0003: A process validation data summary report on the validation of the first three commercial batches will be provided by May 2010, which includes validation of the following maximum hold times: - the time in the compounding tank prior to the bioload reduction filtration - the time in the holding tank prior to the sterile filtration (including transfer of bulk solution) - the time in the surge tank				

Non clinical related FUMs

Nonclinical	**FUM 12** (SIAMED PAC No.FUM3): A proposal to assess the relevance of C-cell adenoma using either non clinical mechanistic studies or other relevant data will be submitted.	31 December 2009	18 December 2009	Fulfilled	18 March 2010 EMA/CHMP/189166/2010
	FUM 13 (SIAMED PAC No.FUM4): Submission of the report of study 670220	30 September 2009	30 September 2009	Fulfilled	17 December 2009 EMA/CHMP/3751/2010
	FUM 14 (SIAMED PAC No.FUM5): The results of the genotoxicity studies in which the impurities are studied (chromosome aberration assay and mouse lymphoma assay, CRL Study No 785862 and CRL Study No 786143) as well as the results from the DEREK analysis of the impurities will be provided as soon as available. (If DEREK analysis shows structural alerts for genotoxicity, the impurities concerned will be tested at sufficient levels as described in the Guideline on the limits of genotoxic impurities and the Question & Answer document on the CHMP Guideline on the limits of genotoxic impurities)	30 September 2009	30 September 2009	Fulfilled	17 December 2009 EMA/CHMP/3751/2010

Pharmacovigilance related FUMs

Pharmacovigilance	**FUM 15** (SIAMED PAC No.FUM6): The RMP will be updated to include a specific section on S. Pneumoniae within the description of the potential risk of colonisation leading to superinfection.	Within 60 days of opinion	21 August 2009	Fulfilled	19 November 2009 EMEA/CHMP/791391/2009
	FUM16 (SIAMED PAC No.FUM6): The RMP will be updated with a new potential risk of tumours including C-adenoma.	Within 60 days of opinion	21 August 2009	Fulfilled	19 November 2009 EMEA/CHMP/791391/2009
	FUM 17 (SIAMED PAC No.FUM6): The RMP will be updated to include the following adverse events within the serious hypersensitivity reactions (due to their association with parenteral aztreonam): toxic epidermal necrolysis, purpura, erythema multiforme, exfoliative dermatitis, urticaria, petechiae, pruritus, diaphoresis.	Within 60 days of opinion	21 August 2009	Fulfilled	19 November 2009 EMEA/CHMP/791391/2009
	FUM 18 (SIAMED PAC No.FUM6): The RMP will be updated to include bronchospasm as identified risk and not as a potential risk.	Within 60 days of opinion	21 August 2009	Fulfilled	19 November 2009 EMEA/CHMP/791391/2009

The following **Specific Obligations and Follow-up Measurements** are applicable for this MA since the last renewal as summarised in the letter of undertaking (23 June 2010):

Specific Obligations

Area	**Description:**	**Due Date**
Clinical	**SO1 (SIAMED PAC No.SOB7):** The applicant commits to submit the results of study GS-US-205-0110 in September 2010.	September 2010 **To be submitted**
Clinical	**SO2 (SIAMED PAC No.SOB8):** Ongoing studies (ages 6 years and older): Study GS-US-205-0110: Open-label, randomized Phase 3 study to evaluate the efficacy and safety of AZLI versus Tobramycin Nebulizer Solutions (TNS) in an intermittent aerosolized regimen in patients with CF. The final clinical study report will be available September 2010.	September 2010 **To be submitted**
Clinical	**SO2 (SIAMED PAC No.SOB10):** A review of all paediatric data from controlled studies will be provided by September 2010.	September 2010 **To be submitted**

Follow-up measures

Area[1]	Description	Due date[2]
Quality	**FUM 5**: The applicant will either tighten the prefiltration bioburden limit or submit the bioburden data from drug product manufacturers as proposed for an additional 10 lots of commercial manufacturing experience	31/12/2010
Quality	**FUM 6**: The applicant commits to validating the manufacturing process at the proposed manufacturing sites as outlined in Module 3, Section 3.2.R.1-1, 'Process validation scheme for the manufacture of aztreonam lysine powder for inhalation' prior to commercialization.	31/12/2010
Quality	**FUM 19**: Resultant of variation EMEA/H/C/996/II/0003: A process validation data summary report on the validation of the first three commercial batches manufactured will be provided by May 2010, which includes validation of the following maximum hold times: - the time in the compounding tank prior to the bioload reduction filtration - the time in the holding tank prior to the sterile filtration (including transfer of bulk solution) - the time in the surge tank	31/05/2010

The final clinical study for report **study GS-US-205-110** has been submitted on 29 September 2010. Subsequently, the final study report was assessed (assessment report dated 19 November 2010, Annex 4). Outstanding questions have been posed to the MAH. On 16 March 2011, the MAH responded to these outstanding issues. The response has been assessed in a separate report, circulated on 12 May 2011 (Annex 5) and with a final update provided on 17 June 2011 (Annex 6).

Within this renewal application the MAH submitted a revised letter of undertaking (dated 16 May 2011) that pertains to the follow up measures to be submitted within the specified timeframe:

Area[1]	Description	Due date[2]
Quality Drug product	**FUM 5**: The applicant will either tighten the prefiltration bioburden limit or submit the bioburden data from drug product manufacturers as proposed for an additional 10 lots of commercial manufacturing experienced	30/06/2011
Quality	**FUM 6**: The applicant commits to validating the manufacturing process at the proposed manufacturing sites as outlined in Module 3, Section 3.2.R.1-1, 'Process validation scheme for the manufacture of aztreonam lysine powder for inhalation' prior to commercialization.	30/06/2011

3.2. Specific Obligations – Interim Report

Quality Specific obligations

Not applicable

Non-Clinical Specific obligations

Not applicable

Clinical Specific obligations

Please refer to section 3.3.3.

3.3. Other Scientific Data provided relevant for the assessment of the benefit/risk balance

3.3.1. Quality

No quality information has been submitted.

Since granting the conditional MA the MAH has submitted the following variations:

One **type II variation (0003)** regarding process validation of the diluent production

Furthermore ten (9) 1B variations were submitted after granting the conditional MA.

1B/0001: To extend the shelf-life of the finished product (solvent) from 24 months to 48 months.

1B/0002: To improve the sensitivity of the organic volatile impurity (OVI) test procedure (TM-109) in the active substance, aztreonam.

1B/0004: To change the storage conditions of the active substance aztreonam from 'to be stored refrigerated (2ºC to 8ºC)' to 'to be stored at or below 8ºC. Aztreonam active substance may be stored in a refrigerator or in a freezer.'

1B/0012: To introduce an alternative lyophilization cycle to be used in the manufacture of aztreonam lysine powder for nebuliser solution.

1B/0013: Stability of FP – Extension of the shelf life of the finished product - As packaged for sale (supported by real time data).

1B/0014/G:

- To add an alternative method for residual solvents;
- To add alternative sites responsible for quality control testing of the active substance;
- To add an alternative site responsible for quality control testing of the active substance.

1B/0017: To add an optional (alternate) in-process sampling location point for Aztreonam Lysine Powder for Nebuliser Solution (AZLI).

1B/0019/G:

- To add an additional manufacturing and testing site for Aztreonam Lysine Powder for Nebuliser Solution (AZLI).
- Minor manufacturing change.

1B/0020/G: To add a specified impurity with acceptance criterion in the aztreonam (API) specification and to remove a residual solvent from the aztreonam specification.

3.3.2. Non-Clinical

The MAH confirmed that no new non-clinical data are available since the granting of the initial marketing authorisation.

The following FUMs were undertaken and are considered resolved:

FUM	Issue
FUM 12	C-cell adenoma were observed in the carcinogenicity study. Its relevance needed to be discussed. It was shown that no dose-related increase was observed in combined pre-neoplastic and neoplastic lesions and that the occurrence of C-cell adenoma was still within the historical control range.
FUM 14	Impurities were no qualified regarding genotoxicity. The MAH provided structural alert analysis, an Ames test, a chromosome aberration assay and a mouse lymphoma assay to qualify the impurities.
FUM 13 or 16 *	Information on safety pharmacology was not completed during the registration procedure. A study on the cardiovascular and respiratory systems needed to be submitted post-authorisation. A dog study was provided.
FUM 17	No information on the genotoxicity of aztreonam was provided during registration. Genotoxicity studies with aztreonam needed to be submitted post-authorisation. The MAH provided an Ames test, a chromosome aberration assay and a mouse lymphoma assay.
FUM 18	The environmental risk assessment (ERA) was not completed during the registration procedure. The ERA needed to be completed post-authorisation. The MAH provided the studies with tests that needed to be performed to complete the ERA.

* This FUM was first designated FUM 16 and later FUM 13. It refers however to the same issue (submission of safety pharmacology dog study)

Currently, there are no remaining non-clinical issues left.

3.3.3. Clinical Efficacy

Study CP-AI-006 (completed) and Study GS-US-205-0117 (AIR-CF4) (completed) have been detailed previously (in the first annual renewal report). Hence, the main discussion is focused on **Study GS-US-205-0110**.

Overview of complete phase 3 studies

Study	Design	AZLI Dose	Location	ITT population (treated)	Last patient visit
CP-AI-005 (complete)	Double-blind, placebo-controlled; 28 days TNS (open label) followed by AZLI or placebo	AZLI; 75 mg BID or TID; inhalation; 28-day run-in of TNS, 28 days of AZLI, 56 days of follow-up	**USA 56 sites**	69 BID AZLI, 66 TID AZLI, 38 BID placebo, 38 TID placebo	09/2006
CP-AI-007 (complete)	Double-blind, placebo-controlled	AZLI; 75 mg TID; inhalation; 28 days of AZLI, 14 days of follow-u	**USA, Canada, Australia 53 sites**	80 TID AZLI, 84 placebo	04/2007
CP-AI-006 (complete)	Open-label follow-on study (patients from CP-AI-005 and -007). Patients receive AZLI according to the same regimen (BID or TID) previously assigned in their previous study.	AZLI: 75mg BID or TID; inhalation; Up to nine 28-day courses of AZLI, each course followed by 28 days off treatment		65 BID AZLI 189 TID AZLI	01/2009

Study GS-US-205-0117:

Phase 3, double-blind, multi-centre, multinational randomized, and placebo-controlled trial evaluating AZLI in patients with cystic fibrosis, mild lung disease, and PA.

Study GS-US-205-0117 (AIR-CF4) was assessed before in the previous assessment, in the context of the first renewal of the conditional Marketing Authorisation.

For the completed, ongoing and planned clinical studies involving paediatric patients with CF and *PA* infection refer to the following table.

Completed, Ongoing, and Planned Clinical Studies of ZLI in Paediatric Patients with CF and *PA* Infection

Protocol/ phase	***Indication***	***Primary endpoint***	***Study design***	***Dosage, regimen***	***No. of pts***	***Age criterion***	***No. AZLI pts < 18 yrs***	***Treatment duration***	***Study status***
CP-AI-002 Phase 1B	CF	Safety, tolerability, pharmacokinetics	Double-blind, randomized, placebo-controlled, ascending dose in two age cohorts	AZLI or placebo, 75, 150, 225 mg	AZLI = 23 Placebo = 12 **Total: 35**	≥ 18 yrs ≥ 13 to < 18	13-17 = 11	3 days AZLI	Completed
CP-AI-003 Phase 2	CF and *PA*	% change in FEV_1 (Day 0 to 14)	Double-blind, randomized, placebo-controlled	AZLI or placebo, 75 mg BID, 225 mg BID	AZLI 75 mg = 37 AZLI 225 mg = 37 Placebo = 31 **Total: 105**	≥ 13 yrs	13-17 = 21	14 days AZLI	Completed
CP-AI-005 Phase 3	CF and *PA*	Time to need for inhaled or IV antipseudomonal antibiotics.	Double-blind, randomized, placebo-controlled; 28 days TNS (open label) followed by AZLI or placebo	AZLI or placebo, 75 mg BID or TID	AZLI BID = 69 AZLI TID = 66 Placebo BID = 38 Placebo TID = 38 **Total: 211**	≥ 6 yrs	**< 18 = 34** 13-17 = 25 6-12 = 9	28-day run-in of TNS, followed by 28 days AZLI	Completed

Protocol/ phase	***Indication***	***Primary endpoint***	***Study design***	***Dosage, regimen***	***No. of pts***	***Age criterion***	***No. AZLI pts < 18 yrs***	***Treatment duration***	***Study status***
CP-AI-006 Phase 3	CF and *PA*	AEs, airway reactivity, vital signs, labs	Long-term open-label follow-on from 005 and 007 continuing same regimen as in prior study	AZLI, 75 mg BID or TID	AZLI BID = 85 AZLI TID = 189 **Total: 274**	≥ 6 yrs	**< 18 = 55** 13-17 = 37 6-12 = 18	Up to nine courses of 28-days-on, 28-days-off AZLI	Completed
CP-AI-007 Phase 3	CF and *PA*	Change in CFQ-R respiratory symptoms domain (Days 0 to 28).	Double-blind, randomized, placebo-controlled	AZLI or placebo, 75 mg TID	AZLI = 80 Placebo = 84 **Total: 164**	≥ 6 yrs	**< 18 = 21** 13-17 = 10 6-12 = 11	28 days AZLI	Completed
GS-US-205-0117 Phase 3	CF, *PA*, and mild lung disease	Change at Day 28 from baseline in respiratory symptoms domain of CFQ-R	Double-blind, randomized, placebo-controlled	AZLI or placebo, 75 mg TID	AZLI = 70 Placebo = 70 **Total: 140 planned**	≥ 6 yrs	**< 18 = 42** 13-17 = 28 6-12 = 14	Three courses of 28-days-on, 28-days-off AZLI	Completed
GS-US-205-0110 Phase 3	CF and *PA*	Relative change in FEV_1 % predicted at Day 28 compared to baseline	Open-label, randomized, active-controlled, parallel group	AZLI, 75 mg TID TNS, 300 mg BID	AZLI = 120 TNS = 120 **Total: 240 planned**	≥ 6 yrs	**< 18 = 28** 13-17 = 20 6-12 = 8	Three courses of 28-days-on, 28-days-off AZLI or TNS	Completed
EA-US-205-0111	CF and *PA*	Compassionate use for pts with limited tx options and at risk for disease progression	Open-label expanded access (United States)	AZLI, 75 mg TID	Total: no limit **Current total: 470***	≥ 6 yrs	**< 18 = 84** 13-17 = 63 6-12 = 21	Repeated courses (28-days-on, 28-days-off) of AZLI	**Ongoing**
EA-US-205-0122	CF and *PA*	Compassionate use for pts with limited tx options and at risk for disease progression	Open-label expanded access (Canada)	AZLI, 75 mg TID	Total: 150 planned **Current total: 9***	≥ 6 yrs	**< 18 = 0** 13-17 = 0 6-12 = 0	Repeated courses (28-days-on, 28-days-off) of AZLI	**Ongoing**
GS-US-205-0162	CF and Initial *PA* Infection	Proportion of patients with *PA* negative cultures during all timepoints till 6 months after cessation	Open-label, randomized, no comparator	AZLI, 75 mg TID	Total: 60 planned	3 mos to 17 yrs	**< 18 = 60**	28 days AZLI, with FU 6 months	**Planned**
GS-US-205-XXX2	CF and Initial *PA* Infection	Change in FEV_1 % predicted at various timepoints till 24 months FU	Open–label, randomized, active controlled 28-day tx with 24 months FU	AZLI, 75 mg TID AB against *PA*	Total: 80 planned (stratified)	3 mos to 17 yrs	**< 18 = 80**	One course of 28-days-on AZLI or active AB against *PA;* FU 24 months	**Planned**
GS-US-205-0160	CF and Chronic *PA* Infection	% discontinued for safety /tolerability at Day 168	Open–label	AZLI, 75 mg TID 3 courses (28 days on /28 days off)	Total: 50 planned	< 13 years	**< 13 = 50**	Three courses of 28-days-on AZLI (study duration 7 months)	**Planned**

GS-US-205-0110

Study GS-US-205-0110 is a Phase 3, open-label, multi-centre, randomized, parallel group study comparing the safety and efficacy of Cayston and TNS in adult and paediatric patients with CF aged 6 years or older with pulmonary *PA* infection. The study protocol was amended (communicated earlier to the European Medicines Agency) to accommodate additional requirements asked by the US FDA as outlined below:

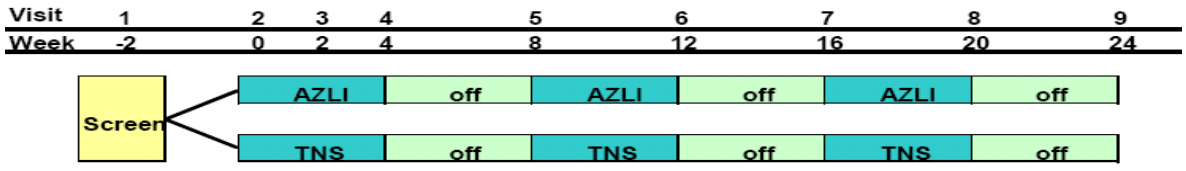
1. The analysis plan was revised to include co-primary endpoints. The non-inferiority endpoint requested by the EMA from the original analysis was maintained. A superiority co-primary endpoint was added, as requested by the FDA.
2. Secondary endpoints were revised based on an updated analysis plan.
3. The sample size was increased to 240 patients in order to adequately power the co-primary and secondary analyses.

Enrolment was closed on 23 October 2009. A total of 273 patients were randomised in the study. Therefore, additional time was requested to enable the extra recruited patients to complete the study and permit supplementary analysis of the final study data. The final CSR has been submitted to the CHMP on 29 September 2010.

The final study report for Study GS-US-205-0110 was submitted on 29 September 2010 as in the context of Specific Obligation 2 (SO 2).

A total of 91 sites participated in this study, across the European Union (62 sites in the EU) and the United States (29 sites in the US). Study ended in May 2010 (last subject visit).

The study design consisted of two treatment arms of 28-day intermittent, repeating-treatment regimens: Aztreonam lysine (AZLI) or Tobi (TNS, Tobramycin Nebuliser Solution) according to the following scheme.



The total study period was to be 26 weeks.

AZLI 75 mg (1 ml) was administered TID via the PARI Investigational eFlow Nebulizer System.

TNS 300 mg (5ml) was administered BID via the PARI LC PLUS™ Nebulizer with Compressor in accordance with the approved labelling.

A short acting bronchodilator was administered before every AZLI or TNS dose. The first dose of AZLI or TNS was administered at the clinic during Visit 2. After the first dose, patients self-administered each AZLI or TNS course of treatment at home for a total of 28 days.

Randomisation was done via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) with equal allocation to one of two treatment regimens.

If at any time after randomisation, the physician determined that a subject required anti-PA antibiotics in addition to the study-provided AZLI or TNS, the subject was required to come to the clinic for an unscheduled visit. In addition to the unscheduled visit procedures, the reason for need of additional anti-PA antibiotics was to be documented. Reasons for administering additional antibiotics could include one or more of the following clinical symptoms associated with development of an acute pulmonary exacerbation:

- Decreased exercise tolerance
- Increased cough
- Increased sputum/chest congestion
- Decreased appetite

The subject was allowed to continue study participation.

Patients receiving AZLI were instructed to administer a BD prior to taking each dose of AZLI at home. Beginning at Visit 2, all patients administered a short-acting BD in the clinic prior to spirometry.

Main inclusion criteria were: Male or female CF patients aged ≥ 6 years with CF, FEV1 < 75% predicted at screening, and PA present in expectorated sputum or throat swab culture within the 3 months prior to screening. Patients must have received previous treatment with aerosolized antibiotics without demonstration of drug intolerance. Patients must have not initiated or changed azithromycin treatment within 28 days of screening.

Main exclusion criteria were:

- History of sputum or throat swab culture yielding B. cepacia in the previous 2 years
- Current use of oral corticosteroids in doses exceeding the equivalent of 10 mg prednisone a day or 20 mg prednisone every other day
- Current requirement for daily continuous oxygen supplementation or requirement for more than 2 l/minute at night
- Administration of any investigational drug or device within 28 days of Visit 1 or within 6 half-lives of the investigational drug (whichever is longer)
- Known local or systemic hypersensitivity to monobactam antibiotics
- Changes in or initiation of chronic azithromycin treatment within 28 days prior to Visit 1
- Administration of anti-PA antibiotics by inhalation, intravenous or oral routes within the 14 days prior to Randomization/Visit 2
- Changes in antimicrobial, bronchodilator (BD), dornase alfa, or corticosteroid medications within 7 days prior to Visit 1
- Changes in physiotherapy technique or schedule within 7 days prior to Visit 1
- History of lung transplantation
- Abnormal renal or hepatic function or serum chemistry at Visit 1

At Visit 1, concurrent medications and therapies including airway clearance techniques were recorded. All medications and treatments, including any changes during the course of the study, were recorded on the Concomitant Medications and Therapies electronic Case Report Form (eCRF).

Patients were to be assessed at Days 14 and 28 during the first course of treatment, then every 28 days for the remainder of the study.

Eligible patients were stratified by disease severity (FEV1 ≤ 50% or > 50% predicted at Visit 1) and inhaled tobramycin use in the previous 12 months (≥ 84 days or < 84 days) and randomized with equal allocation to AZLI or TNS. Patients must have received ≥ 84 days (3 courses) of inhaled tobramycin in the previous 12 months. The criterion < 84 days (3 courses) of inhaled tobramycin stratum was closed by the time US sites were open. The target for randomized patients was approximately 240 with no more than 40 patients having < 84 days use of inhaled tobramycin in the previous 12 months.

A total of 268 patients were randomized and treated (136 AZLI, 132 TNS) in the study.

The following **Co-primary efficacy endpoints** were used:

- Relative change from baseline in FEV1 percent predicted at Day 28 among all patients (non-inferiority analysis)
- Actual change from baseline in FEV1 percent of predicted across 3 treatment courses among all patients (superiority analysis).

The following **Secondary efficacy endpoints** were used:

- Relative change from baseline in FEV1 percent predicted at Day 28 in patients who received inhaled tobramycin for ≥ 84 days in the 12 months prior to randomization (non-inferiority analysis)
- Actual change from baseline in FEV1 percent predicted across 3 treatment courses in patients who received inhaled tobramycin for ≥ 84 days in the 12 months prior to randomization (superiority analysis)
- Time to need for IV anti-PA antibiotic for respiratory events among all patients (superiority analysis)
- Time to first respiratory hospitalization among all patients (superiority analysis) Tertiary endpoints:
- Change from baseline in FEV1 percent predicted at each study visit (exclusive of Day 28)
- Change from baseline in FEV1, FVC, and FEF25-75 at each study visit
- Change from baseline in Cystic Fibrosis Questionnaire Quality of Life – Revised (CFQR) Respiratory Symptoms Scale (RSS) score 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 anti-PA 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)
- Change in PA CFUs in sputum at the end of each on-drug cycle

Additional microbiology assessments included (1) change in *PA* CFUs in sputum over 3 courses of study drug treatment; (2) disappearance or appearance of other respiratory pathogens *(S. aureus, B.*

cepacia, S. maltophilia, A. xylosoxidans, Aspergillus spp.) at each study visit; and (3) change in MIC of aztreonam, tobramycin, and other antibiotics for *PA* at each study visit.

Spirometry was performed according to American Thoracic Society (ATS) guidelines at each visit and FEV1, FVC, and FEF25-75 were recorded. Participants performed at least 3 spirometry manoeuvres that achieved ATS standards. The best FEV1 and FVC were recorded, even if from different efforts. The value recorded for FEF25-75 was taken from the effort that produced the highest sum of FVC plus FEV1 values.

At Visit 2, spirometry was repeated at 30 minutes post-AZLI or TNS treatment. If a subject experienced a decrease in FEV1 (L) of 15 % or more from the pre-treatment value, spirometry was repeated at 60 minutes post-treatment, and every 30 minutes thereafter until the investigator felt it was safe to discharge the subject.

CFQ-R: All patients, and parents of children 6 to 13 years of age, were asked to complete the CFQ-R at Visits 2 through 9 and ET. The same parent completed the CFQ-R at every visit. The CFQ-R is a CF-specific quality of life measure encompassing both generic and CF-specific domains. The translations of the questionnaire into the languages of all participating countries were validated prior to the study. The questionnaire domains include physical functioning, role limitations/school performance, vitality, emotional functioning, social functioning, body image, eating disturbances, treatment burden, health perceptions, weight, respiratory symptoms, and digestive symptoms. The number of domains varies depending on the CFQ-R version being used. The four versions include:

The **safety** evaluation included monitoring of adverse events (AEs), airway reactivity (pre- and post study drug spirometry), vital signs, serum chemistry, and haematology were evaluated.

The **Per Protocol (PP)** analysis set included patients who:

1. Were randomized into the study, **and**
2. Received at least one dose of study medication, **and**
3. Did not violate any major entry criteria (inclusion criteria 1-6 and exclusion criteria 8-9), **and**
4. Did not take any other investigational drug or device and with a relative treatment compliance of at least 50% between Day 0 and Day 28.

Sensitivity analyses of the primary efficacy endpoints were performed on the per-protocol analysis set.

The protocol-specified co-primary ANCOVA analysis of arithmetic average across 3 treatment periods based on predicted values was performed as a sensitivity analysis for the ITT population. This analysis used an ANCOVA model including terms for treatment, FEV1 percent predicted at Visit 2 (as a continuous variable), and inhaled tobramycin use in the previous 12 months (≥ 84 days or < 84 days) to test for treatment differences in the average actual change in FEV1 percent predicted across 3 treatment courses. The arithmetic average was calculated based on predicted values of actual change inFEV1 percent predicted at Visits 4, 6, and 8.

The actual change values at each post-baseline visit (Visit 3, 4, 5, 6, 7, 8, and 9) from baseline were fitted into this model to obtain predicted values.

As additional sensitivity analyses, in order to evaluate the long-term overall performance of AZLI against TNS for the primary superiority endpoint on the ITT population, statistical comparisons based on LS means at each of the post baseline visits (Visit 3, 4, 5, 6, 7, 8, and 9) from the primary MMRM model were performed. For these analyses, it was expected that AZLI should be at least numerically superior to TNS at the end of each treatment course (Visits 4, 6, and 8 respectively).

The last observation carried forward (**LOCF**) approach was used to impute missing post-baseline data values for spirometry and CFQ-R data. As an example of the LOCF method, if a subject had a missing value at Day 28, then the latest available value among Day 0, Day 14 and ET was used; if a subject had a missing value at Week 20, then the latest available value including ET from Day 0 up to Week 16 was used; if a subject had a missing value at Week 24, then the latest available value including ET from Day 0 up to Week 20 was used. The LOCF method was also used for weight and body mass index (BMI) data; however, only missing values at Week 24 were imputed.

As a supportive analysis of the change from baseline in FEV1 percent predicted, the less favourable of two group means method (LF) was used to impute missing post-baseline data for the visit at which the data was missing. For example, if a subject had a missing value at Day 8, then the smaller value of the two group means was assigned to this subject regardless of the treatment.

As an exploratory analysis, the potential for interaction between treatment group and previous inhaled tobramycin use was examined for spirometry, CFQ-R, and CFU data. The descriptive statistics for AZLI and TNS treatment groups under previous inhaled tobramycin use was visually evaluated.

For the time to need for IV anti-PA antibiotics for respiratory events a sponsor-independent, blinded review committee reviewed the IV anti-PA antibiotics and identified the subset used for respiratory events. The committee adjudicated events based on AE/SAE reports, concomitant medications, baseline characteristics and demographics, and other relevant data as determined necessary by the committee. This independent committee approach was performed also for the evaluation of time to first respiratory hospitalization

There were 22 amendments to the original EU protocol (Version 1.0, dated 07 September 2007), and 3 amendments to the original US protocol (Version 4.4, dated 07 April 2009).

The majority of these amendments/versions were country-specific variations of amendments to the initial protocol.

GCP: The study report mentions that the trial was conducted in accordance with the GCP guideline.

CRO was Chiltern International Ltd (UK).

Compliance: Patients were required to use at least 50% of each of the allocated treatments. Patients who used less than 50% of any one course were discontinued from the study.

RESULTS

Disposition of patients

Twenty-five TNS-treated patients discontinued the study (12 withdrew consent), and 25 discontinued study drug (12 withdrew consent). Three patients in the AZLI group and 5 patients in the TNS group discontinued the study drug for safety or tolerability reasons.

A total of 62 important protocol deviations involving 55 patients occurred during the study.

Demographic and Other Baseline Characteristics

Patients ranged in age from 6 to 69 years, with a mean (SD) age of 25.5 (9.0) years. One hundred thirty-four (50.0%) patients were female. Two hundred sixty-one (97.4%) patients were white. Ninety-four patients (35.1%) were enrolled at US sites. One hundred seventeen patients (43.7%) had a baseline disease severity of FEV1 ≤ 50% predicted. Overall mean (SD) baseline FEV1 % predicted, CFQ-R RSS score, and log10 *PA* CFUs were 52.27 (15.06), 60.44 (20.69), and 6.16 (2.41), respectively. See further the following table.

Demographic and baseline characteristics were generally balanced between treatment groups.

CFQ-R RSS score and log10 CFUs: The mean (SD) CFQ-R RSS score for patients treated with AZLI was 62.87 (20.42) compared to 58.02 (20.76) for those treated with TNS which approached statistical significance (p = 0.057). The mean (SD) log10 CFUs for patients treated with AZLI was 6.39 (2.07) compared to 5.93 (2.70) for those treated with TNS (p = 0.175).

Demographic and baseline characteristics for patients by previous inhaled tobramycin use were similar to the overall population.

Compliance results

The overall mean percent of vials used greater than 90% for both treatment groups for all courses No differences were noted across treatment courses with the.

Efficacy results

The results for the (co-)primary endpoints i.e. the adjusted mean relative change from baseline in FEV1 % predicted at Day 28 show that AZLI was at least as efficacious as TNS after 1 or 3 cycles:

- relative change FEV1 after 28 days (non inferiority): 8.35 vs 0.55 (-7.8 difference therefore AZLI non-inferior using a 4% non-inferiority margin)
- Actual change from baseline in FEV1 percent of predicted across 3 treatment courses: 2.05 vs -0.66.

Table: Change from baseline in FEV1 % predicted at Day 28 after 1 cycle and 3 cycles- Non-inferiority and Superiority Analysis (ITT Population)

Endpoint	AZLI (N = 136)	TNS (N = 132)	Treatment difference TNS-AZLI (95% CI)	p-value
Adjusted mean (SE)[a] Relative Change from Baseline in FEV1 % Predicted at Day 28 (Week 4)	8.35 (1.70)	0.55 (1.77)	-7.80 (-11.73, -3.86) Non-inferiority	0.0001
Adjusted mean (SE)[b] Average of Actual Change of FEV1 % Predicted at Visit 4, Visit 6, and Visit 8	2.05 (0.69)	-0.66 (0.72)	-2.70 Superiority	0.0023
Sensitivity Analysis of Primary Superiority Endpoint				
Adjusted mean (SE)[a] Average of Actual Change of FEV1 % Predicted at Visit 4, Visit 6, and Visit 8 based on Predicted values	2.19 (0.52)	-0.53 (0.72)	-2.72	<0.0001

LOCF method is used to impute missing data for non-inferiority analysis.
a Adjusted means from ANCOVA model including treatment, Visit 2 FEV**1** % predicted, and previous inhaled tobramycin use for all patients.
b Adjusted means from MMRM model including Visit 2 FEV**1** % predicted, previous inhaled tobramycin use, treatment, visit, and treatment/visit interaction for all patients

The treatment difference after 28 days of treatment met the chosen upper boundary < 4 for non-inferiority of AZLI to TNS.

Similarly, the treatment difference in the adjusted mean actual change from baseline in FEV1 % predicted at Visits 4, 6 and 8 (superiority analysis) was -2.70 in favour of AZLI-treated patients.

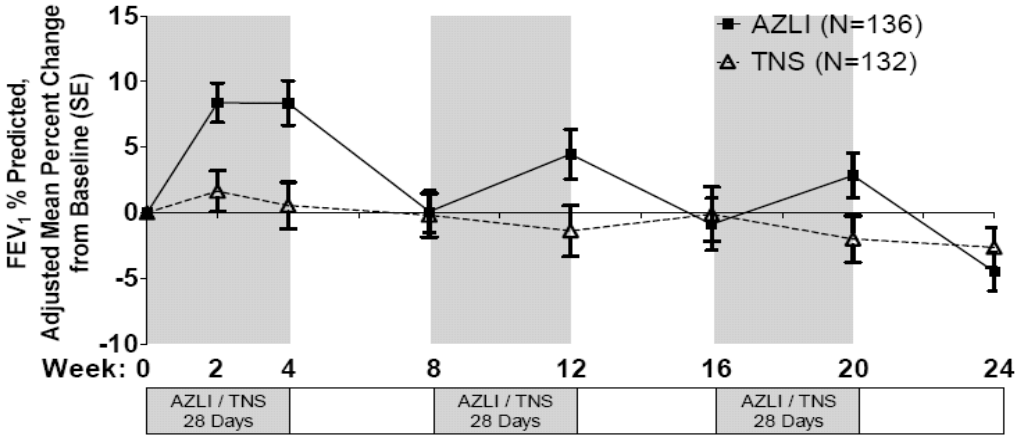
The PP analysis gave similar results.

Table: Change from baseline in FEV1 % predicted at Day 28 after 1 cycle and 3 cycles- Non-inferiority and Superiority Analysis (PP Population)

Endpoint	AZLI (N = 136)	TNS (N = 132)	Treatment difference TNS-AZLI (95% CI)
Adjusted mean (SE)[a] Relative Change from Baseline in FEV1 % Predicted at Day 28 (Week 4)	8.60 (1.72)	0.75 (1.79)	-7.86 (-11.88, -3.84) Non-inferiority
Adjusted mean (SE)[b] Average of Actual Change of FEV1 % Predicted at Visit 4, Visit 6, and Visit 8	2.05 (0.69)	-0.58 (0.73)	-2.6 Superiority

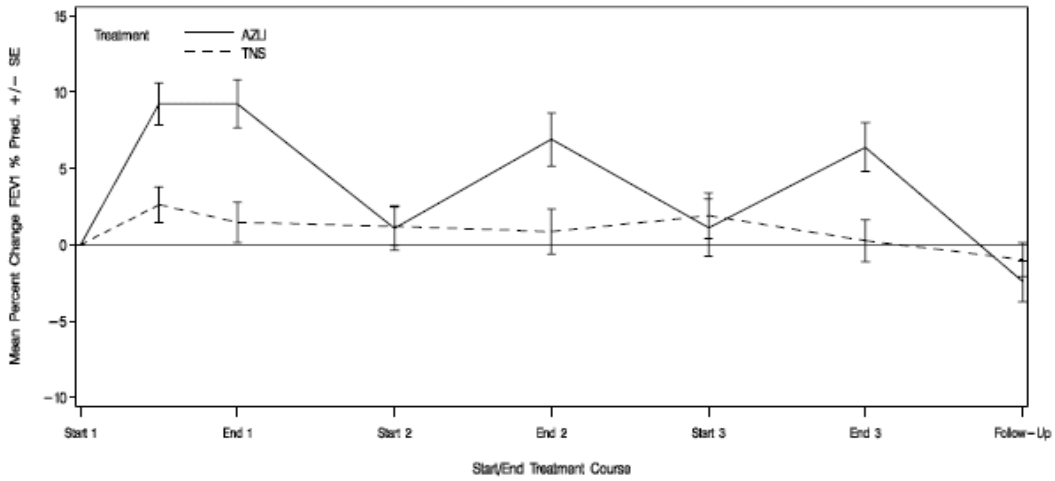
Attenuation of change in FEV1 % predicted was observed following repeated courses of therapy in both the AZLI and TNS treatment groups.

Figure 1. **FEV_1 % Predicted Change from Baseline on Imputed Data by LOCF (Mean Change and SE)**



Further analyses of the FEV1 % predicted data using observed case data are displayed in the following figure.

Figure 2: Percent Change in FEV1 % Predicted from Baseline on Observed Case Data (ITT Population)



Similar patterns have also been observed for LOCF analysis (percent change, actual change), and LF analysis as documented in the study report.

This attenuation is considered by the MAH to be unlikely due to the development of resistance, as no concerning changes in *PA* susceptibility to aztreonam or tobramycin were observed among patients in either treatment group in this study (see section on Additional microbiological results). Rather, seasonality provides a possible explanation, as the majority of the patients in both treatment groups enrolled during the summer months and received their second and third treatment courses during the fall and winter months. The diminished improvements in lung function among patients receiving treatment during the fall and winter months might be attributed to concomitant viral infections. Similar seasonality effects have been observed in the AZLI Study CP-AI-007 provided in the original MAA, as well as in studies of other inhaled antibiotics.

Secondary and tertiary endpoints

Significant improvement in CFQ-R RSS (Quality of life score), fewer hospitalizations (40 vs 58, p=0.04), fewer requirements for anti-pseudomonas inhalation or intravenous antibiotic therapy (84 vs 121, p=0.004) and longer time to need for these antibiotics.

Change in CFU was non-significant (-0.55log vs -0.32log, p=0.3). No significant differences in adverse events in this open label study were observed.

This study demonstrated an improvement of FEV1 predicted at the end of each AZLI treatment course with less hospitalizations and requirements for additional anti-pseudomonal treatment in cystic fibrosis patients, but also that:

- In Tobramycin-naïve patients (less than 84 days of Tobramycin inhalation in the previous 12 months) better lung function as measured by FEV1 was achieved with Tobramycin than with AZLI:
  - primary endpoint at day 28: 2.45 vs. 4.65 relative change in FEV1
  - primary endpoint as average of actual change across 3 courses: -1.33 vs. 0.51
- Also in this group of Tobramycin-naïve patients numerically less hospitalizations and requirements for IV or inhaled anti-pseudomonal antibiotics for respiratory events were recorded in the AZLI treated patients.

- In strains exposed to Aztreonam MIC to Aztreonam increased > 4-fold whereas Tobramycin MIC90 did not increase and in more AZLI-treated subjects strains were isolated with MIC for the study drug that increased 4 fold during the study time and did not reverse in off-treatment periods in the AZLI treated subjects than in TNS-treated patients.
- In the AZLI-treated patients more frequent occurrence of decreased susceptibility to beta-lactam antibiotics was demonstrated with increases in MIC90 of cefepime and piperacillin. Also demonstrated was an increase of resistance to all 6 beta-lactam antibiotics (cefepime, ceftazidime, piperacillin, piperacillin/tazobactam, ticarcillin/clavulanic acid, and meropenem) in at least one isolate of Pseudomonas from baseline to week 24 from 13.0 to 18.4%, while this proportion in Tobramycin treated patients remained stable (17.3-18.8%).
- increase in occurrence of Pseudomonas strains with Aztreonam MIC>8 mg/L from 0 to 24 weeks during treatment: 34% to 49% in AZLI treated patients (again no reversal of MIC during off-treatment periods), whereas the proportion of 35% in Tobramycin-treated patients at week 0 remained always below baseline (max. 32% at end of treatment).
- Resistance to aminoglycosides of Pseudomonas isolates in Tobramycin treated patients increased over 24 weeks: 29.1 to 33.3%

Increase in treatment-emergent isolation of intermittent and persistent MRSA and MSSA : treatment-emergent isolation of MSSA occurred in more AZLI-treated subjects (17% [n=22]) compared to TNS-treated subjects (12% [n=15]). Treatment-emergent isolation of MRSA occurred in more AZLI-treated subjects (10% [n=13]) compared to TNS-treated subjects (1% [n=1]).

Conclusion on study 0110

- In tobramycin experienced patients AZLI improves FEV1 during treatment periods compared to TNS
- No sustained effect is achieved in lung function improvement because at week 24 patients return to baseline FEV1 values comparable to TNS, but non-inferiority at the 6 months evaluation point was demonstrated.
- In tobramycin experienced patients, AZLI reduces significantly the need for additional antibiotic treatment and hospitalization during on-treatment and off-treatment periods
- In tobramycin experienced patients, AZLI achieves improvement in lung function also in case of increased Aztreonam MICs or beta-lactam resistance and preserves lung function in case of MDR PA during treatment, but data is not provided whether this improvement or preservation also required additional antibiotics in the AZLI group.
- In the tobramycin naïve patients, AZLI does not significantly improve lung function compared to TNS and data on the reduction of the need for additional antibiotic treatment are not provided, but considering the small sample size of this subgroup in this study the identification of significant findings that can be extrapolated to all tobramycin naïve patients is unlikely.

3.3.4. Clinical Safety

The safety of Cayston was described in the original Assessment Reports and supports the conditionally approved dose of 75 mg Cayston TID. Nine adverse drug reactions (ADRs) were considered to be reasonably associated with the use of Cayston: cough, nasal congestion, wheezing, pharyngolaryngeal pain, pyrexia, chest discomfort, rhinorrhea, non-allergic bronchospasm, and rash. All of the ADRs were typical for patients with CF lung disease.

Subsequent to submitting the Cayston Marketing Authorisation Application, 3 studies that evaluated the safety of Cayston have been completed (**CP-AI-006, GS-US-205-0117** and **GS-US-205-0110**) and 2 studies are currently on-going (**EA-US-205-0111 and EA-US-205-0122**).

GS-US-205-0110 (completed)

In the aztreonam lysine (AZLI) group, 130 subjects (95.6%) experienced a total of 1360 Adverse Events (AEs). In the Tobi (TNS) group, 128 subjects (97%) reported a total of 1341 AEs. Respiratory AEs were the most frequently reported AEs. Most commonly cough was reported (AZLI 96 subjects, TNS 104 subjects), followed by productive cough (AZLI 70 subjects, TNS 104 subjects), oropharyngeal pain (AZLI 36 subjects, TNS 37 subjects) and dyspnoea (AZLI 32 subjects, TNS 36 subjects). Hemoptysis occurred more frequently among AZLI-treated subjects (31) as compared to TNS-treated subjects (21).

Thirty-one (31) subjects in the AZLI group and 17 subjects in the TNS group experienced AEs that were assessed as related to study drug, with the majority of these subjects experiencing respiratory AEs.

Three subjects in the AZLI group experienced drug-related serious adverse events (compared to none in the TNS group). All 3 cases reported respiratory events. Two subjects experienced wheezing and 1 subject experienced productive cough, dyspnoea, hemoptysis and discoloured sputum.

Nine subjects treated with AZLI discontinued due to an AE. 6 subjects treated with AZLI and 1 subject treated with TNS discontinued due to respiratory AEs. The most frequent AEs leading to discontinuation were cough and hemoptysis (each 3 subjects).

The MAH concludes that in study GS-US-205-0110 AZLI was well tolerated over 3 treatment courses with an AE profile consistent with the previously established experience for AZLI.

Ongoing Safety Studies (EA-US-205-0111; EA-US-205-0122)

In addition to the completed studies, the safety of AZLI is being evaluated in 2 expanded access programmes, **EA-US-205-0111** and **EA-US-205-0122**.

The combined safety results as of the last data analysis cut-off of 03 May 2010 are presented here. In study EA-US-205-0111 a total of 570 subjects had enrolled and 544 subjects had received at least 1 dose of AZLI. Study EA-US-205-0122 is currently enrolling with 34 subjects enrolled as of 31 January 2011.

A total of 44 subjects have discontinued due to SAE (35 with a pulmonary exacerbation or end-stage CF lung disease, 5 with pneumothorax, and 4 with hemoptysis). Additionally there have been 24 deaths. Reported causes of death included respiratory failure, lung disorder, cystic fibrosis, cardio-

respiratory arrest, pneumonia, pneumothorax, cystic fibrosis lung, acute respiratory failure, hemoptysis, arterial hemrorrhage, pneumonia necrotising, sepsis, multi-organ failure, shock and cardiac arrest. None of the deaths were judged to be related to treatment by the investigators.

307 subjects experienced a total of 793 severe adverse events (SAEs). Three were considered drug related by the investigator (pulmonary exacerbation, hemoptysis, and spontaneous abortion). The most commonly reported SAEs (> 1% of the subjects) were consistent with the underlying disease and consisted of the following: Lung disorder (264 subjects), hemoptysis (22 subjects), cystic fibrosis lung (12 subjects), pneumonia (9 subjects), pneumothorax (9 subjects) and small intestinal obstruction (6 subjects).

3.3.5. Post-Marketing Experience

Postmarketing safety data are available from the second PSUR (reporting period from 12 Mar 2010- 11 Sep 2010).

Summary of PSUR 2

Marketing exposure

Since first approval, cumulative post-marketing exposure in US, Canada and EU is estimated to be 6,048 patient-months of treatment and exposure to AZLI was estimated as 5,701 patient-months during the period of the PSUR. The exposure in the EU is 585 patient-months.

Indication

Differences exist in indications between different countries world-wide:

- In the EU, Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to PA in patients with CF aged **18 years and older**.
- In Australia, Cayston is indicated for control of gram-negative bacteria, particularly PA, in the respiratory tract of patients with cystic fibrosis (CF) 6 years and older.
- In Canada, Cayston is indicated for the management of CF patients with chronic pulmonary PA infections in patients aged 6 years and older.
- In the US, Cayston is indicated to improve respiratory symptoms in CF patients with PA aged 7 years and older.

AZLI is also currently in a clinical development program investigating the following:

- Improvement in respiratory symptoms in patients with bronchiectasis and pulmonary gram negative bacteria in patients aged 18 years and older.
- Safety and efficacy of AZLI for suppressive therapy of chronic pulmonary infections due to PA in patients with CF aged 6 years and older.
- Safety and efficacy of continuous AZLI therapy in CF subjects with Burkholderia species infection in the airways.

Adverse events

Twenty-one medically confirmed case reports (20 spontaneous, 1 from clinical trial) were received during the period covered by the PSUR. 5 cases were serious unlisted, one was serious listed, 13 were

non-serious unlisted and two were non-serious listed. The reported medically confirmed AEs are summarised in the table below.

System Organ Class	Serious		Not serious		Total
	unlabelled	labelled	unlabelled	labelled	
Ear and labyrinth disorders			Hearing impaired (1)		1
Gastrointestinal disorders	Swollen togue (1)		Gingival swelling (1)		2
General disorder and administration site conditions	Feeling hot (1)		Asthenia (1) Chest discomfort (1) Chills (1) Discomfort (1) Influenza like illness (1)	Chest discomfort (2) Pyrexia (2)	10
Infections and infestations	Bronchiectasis (1)		Upper respiratory tract infection (1)		2
Investigations			Pulmonary function test decreased (1)		1
Musculoskeletal and connective tissue disorders	Muscle spasms (1)		Arthralgia (4) Back pain (1) Joint swelling (1) Pain in extremity (1) Tendonitis (1)		9
Nervous system disorders	Disturbance in attention (1)		Headache (2)		3
Respiratory, thoracic and mediastinal disorders	Hemoptysis (3) Respiratory failure (1)	Bronchospasm (1)	Dyspnoea (2) Hemoptysis (1)	Bronchospasm (1) Cough (1) Obstructive airways disorder (1) Oropharyngeal pain (1)	12
Psychatric disorders			Mood swings (1)		1
Skin and subcutaneous tissue disorders			Urticaria (1)	Dermatitis acneform (1) Rash generalised (1)	3
Total	9	1	24	10	44

Safety issues under review

During the period covered by this PSUR the following topics of special interest for AZLI were assessed:

- Hemoptysis: During the period under review by the PSUR, four medically confirmed cases of hemoptysis were received. Three of the cases were spontaneous cases (2 serious, 1 non-serious), and the remaining case was a serious adverse event from a clinical trial that was considered related to AZLI by the investigator. All four cases were confounded by progression of the underlying lung disease and in two of the four cases there was a history of hemoptysis prior to AZLI therapy. Also, two of the cases reported a negative rechallenge, which suggests an alternative aetiology.
- Bronchospasm in Patients with Severe Lung Disease: During the PSUR period, 2 cases were reported (1 serious, 1 non-serious). Bronchospasm in patients with severe lung disease is an identified risk in the RMP for AZLI. Bronchospasm is a labelled event in the SmPC.
- Hypersensitivity: During the period under review by the PSUR two cases were received describing allergic type reactions (tongue swelling and generalised rash in one case and hives and joint pain

in the other case). Both cases were considered unrelated to AZLI due to lack of information or due to the reporting physician's causality assessment (not related).

- Pregnancy and Lactation: A total of five pregnancy cases involving AZLI exposure have been reported up to 11 September 2010. During the period under review by the second PSUR one pregnancy outcome for a previously reported case was received. The patient gave birth to a premature female neonate at 34 weeks of gestation. The neonate was noted to have hyperbilirubinemia secondary to premature birth and was admitted to rule out sepsis. The neonate was noted to have congenital abnormalities including mild congenital hypothyroidism and congenital adrenal hyperplasia. The neonate was discharged 11 days later. The investigator assessed the pregnancy outcome as unrelated to the study drug as well as unrelated to the concomitant medications and stated that the patient's medical condition of pre-eclampsia had contributed to this outcome.
- Special patient groups – Children (aged less than 18 years): During the period under review by the PSUR there were two spontaneous reports involving the use of AZLI in patients less than 18 years of age. Both cases originated form the US where AZLi is indicated for use in patients aged 7 years and older. No new safety issue was identified.

Other conclusions

No new safety data was identified regarding: Drug Interactions; Overdose; Drug Abuse or Misuse; Prescription or Medication Errors; Partner Pregnancies; Lactation; Elderly patients; Off-Label Use; Effects of Long-Term treatment Patient/consumer and other non-healthcare professional reports.

– **CHMP comments:**

PSUR2 did not reveal major new safety issues for AZLI at the recommended dosage. The following issues should be continued to be closely monitored: Bonchospasm in patients with severe lung disease; hypersensitivity; severe allergic reactions; reports of the use of AZLI during pregnancy/lactation. Haemoptysis remains a point of concern.

PSUR 3 was submitted by MAH during April 2011. Assessment of RMP 3 is ongoing.

3.3.6. AZLI EU RMP

Summary of AZLI EU RMP Version 2 (April 2010)

Summary Table of the EU Risk Management Plan

Safety Concern	***Agreed pharmacovigilance activities***	***Agreed risk minimisation activities***
Important Identified Risks		
Bronchospasm in patients with severe lung disease	Routine pharmacovigilance activities Review of pulmonary function data in clinical study GS-US-205-0110.	**Proposed SPC text:** **Section 4.4** *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 4.8** *Respiratory, thoracic and mediastinal disorders* Common: non-allergic bronchospasm

Safety Concern	*Agreed pharmacovigilance activities*	*Agreed risk minimisation activities*
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 Review of adverse event data in clinical study GS-US-205-0110.	**Proposed SPC text:** **Section 4.4** *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 4.8** *Skin and subcutaneous tissue disorders* Common: rash 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 Review of adverse event data in clinical study GS-US-205-0110.	**Proposed SPC text:** See above for Serious Hypersensitivity Reactions.
Toxic epidermal necrolysis	Routine pharmacovigilance activities Review of adverse event data in clinical study GS-US-205-0110.	**Proposed SPC text:** See above for Serious Hypersensitivity Reactions.

Safety Concern	***Agreed pharmacovigilance activities***	***Agreed risk minimisation activities***
Colonization leading to superinfection	Routine pharmacovigilance activities Review of microbiology data plus data on prescribed medications, and monitoring of AEs (including pneumonia, meningitis, bacteremia, sinusitis, cellulitis, and otitis media) which might indicate fungal or bacterial superinfections in clinical study GS-US-205-0110	**Proposed SPC text:** **Section 4.4** 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. In clinical studies of Cayston, no increases of clinical significance were observed in the prevalence of antibiotic-resistant *P. aeruginosa* or other bacterial respiratory pathogens among patients treated three times daily with Cayston. Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function were observed following treatment with Cayston. An increased prevalence of *Aspergillus* and *Candida* species were observed over time in patients treated with several Cayston treatment courses. The clinical significance of this finding is unknown. **Section 5.1** *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 Review of susceptibility data in clinical study GS-US-205-0110 Planned prospective observational study linked to US CFF Registry to assess changes in *PA* susceptibility to aztreonam over a 5-year period	**Proposed SPC text:** **Section 4.4** 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. In clinical studies of Cayston, no increases of clinical significance were observed in the prevalence of antibiotic-resistant *P. aeruginosa* or other bacterial respiratory pathogens among patients treated three times daily with Cayston. Among patients with multidrug-resistant *P. aeruginosa*, improvements in respiratory symptoms and pulmonary function

Safety Concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
		were observed following treatment with Cayston. **Section 5.1** *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* - 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

Safety Concern	*Agreed pharmacovigilance activities*	*Agreed risk minimisation activities*
		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 a 28-day course 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, regardless of whether the highest aztreonam MIC for *P. aeruginosa* was above or below the established susceptibility breakpoint for intravenous aztreonam administration (8 µg/ml). Based on categorical analyses of the relationship between MIC and treatment response, a susceptibility breakpoint for Cayston cannot be established. Over 6 courses of Cayston therapy, *P. aeruginosa* MIC_{50} and MIC_{90} did not change (± 2 dilution change), however there is a theoretical risk that patients treated with Cayston may develop *P. aeruginosa* isolates resistant to aztreonam or other beta-lactam antibiotics.
Off-label use in children and adolescent patients (under 18 years of age)	Routine pharmacovigilance activities	**Proposed SPC text:** **Section 4.1** Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 18 years and older. **Section 4.2** *Paediatric population* Cayston is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy (see section 5.1).

Safety Concern	***Agreed pharmacovigilance activities***	***Agreed risk minimisation activities***
Important Missing Information		
Limited safety data in adults (including long term safety)	Routine pharmacovigilance activities. Review of safety data from clinical study GS-US-205-0110, expanded access programs (EA-US-205-0111, EA-US-205-0122), and a new planned clinical study comparing twice-daily with three-times daily AZLI (protocol under development).	N/A
Limited safety data in children	Routine pharmacovigilance activities Review of safety data from clinical study GS-US-205-0110, expanded access programs (EA-US-205-0111, EA-US-205-0122), two planned pediatric studies (proposed in the AZLI Pediatric Investigation Plan) and a new planned clinical study comparing twice-daily with three-times daily AZLI (protocol under development). A review of all pediatric data from controlled clinical studies	N/A

The RMP Version 2 (April 2010) was updated to Version 3 (submission: April 2011).

The most relevant change noted in the update was as follows:

- The AZLI EU-RMP was updated with new safety data from the randomised phase of Study GS-US-205-0110 where the safety and efficacy of 3 repeated 28-day cycles of AZLI therapy compared to tobramycin nebuliser solution (TNS) were evaluated. A total of 136 patients received AZLI in the study including 28 children aged 6 to 17 years. No new safety concerns for AZLI in adult and pediatric subjects were identified and there were no reports of serious hypersensitivity reactions, anaphylaxis or toxic epidermal necrolysis. There was also no evidence of superinfection or the development of resistance, with clinical sequelae, to aztreonam or other antibiotics. One patient developed an acute decrease of > 15% in FEV1 30 minutes following dosing with AZLI; however, no symptoms or adverse events associated with this episode of airway reactivity were reported and the patient was not withdrawn from the study.

Other significant changes to the Cayston-RMP include the following:

- *Paediatric summary*: In Phase 2 and Phase 3 placebo-controlled clinical studies of AZLI, pyrexia was observed at a higher incidence rate in paediatric subjects aged 6 to 17 years (18%) compared to adults (8%). The EU-RMP was updated to include a review of all paediatric data from controlled

clinical studies including the randomised phase of the active controlled study GS-US-205-0110. In this study, the incidence of pyrexia was higher in paediatric subjects than adults and similar in paediatric subjects who received AZLI and those who received TNS. No new safety concerns for AZLI in pediatric subjects aged 6 to 17 years were identified.

- *AZLI Paediatric Investigation Plan (PIP)*: The Cayston EU-RMP was updated in line with the AZLI PIP that was approved by the Agency on 29 October 2010. The approved Cayston PIP includes an exploratory Phase 2 study (GS-US-205-XXX1 [GS-US-205-0162]) and a deferral to conduct a subsequent Phase 3 study (GS-US-205-XXX2) to evaluate initial *PA* infection in pediatric subjects (aged 3 months to 17 years), and 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 study GS-US-205-0110, which included children with CF 6 years or older. These studies will provide additional safety data in children.

The assessment report on RMP 3 will be adopted by CHMP during its July 2011 meeting.

3.4. Product Information

3.4.1. Summary of Product Characteristics, Labelling and Package Leaflet

The MAH proposed changes to the Product Information (PI), conform the latest QRD-template. Generally, proposed changes are accepted. Detailed comments are provided hereafter.

- **CHMP comments:**

Summary of Product Characteristics

Section 4.6 fertility, pregnancy and lactation

CHMP's comment: in section 4.6 "fertility' was introduced in the heading conform QRD. The CHMP proposes to include the following text in this section:

Fertility
Data about fertility do not indicate any adverse effects.

The MAH complies with the request and in agreement with CHMP introduces a slightly amended phrase: "Non-clinical data for aztreonam for injection about fertility do not indicate any adverse effects."

Section 4.8 Undesirable effects

The MAH proposes the following changes to update section 4.8:

a. Summary of the safety profile

The safety of Cayston was evaluated in three Phase 3 studies in 344 predominantly adult patients (77%) with chronic *P. aeruginosa*. 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 CF patients received up to nine 28-day treatment courses of Cayston 75 mg 2 times or 3 times a day.

In the two Phase 3 placebo-controlled clinical trials, the most frequently occurring adverse reactions to Cayston were cough (58%), nasal congestion (18%), wheezing (15%), pharyngolaryngeal pain (13.0%), and pyrexia (12%).

An acute reduction of ≥ 15% in FEV1 is a complication associated with nebulised therapies, including Cayston (see section 4.4).

b. Tabulated summary of adverse reactions

The adverse reactions with suspected (at least possible) relationship to treatment in the placebo controlled studies are listed below by body system organ class and frequency.

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

Respiratory, thoracic and mediastinal disorders:
Very common: wheezing, cough, pharyngolaryngeal pain, nasal congestion
Common: non-allergic bronchospasm1, chest discomfort, rhinorrhoea
Skin and subcutaneous tissue disorders:
Common: rash[1]
General disorders and administration site conditions:
Very common: pyrexia
[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 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 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).

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.

CHMP's comment: The proposed changes are accepted.

Section 5.1 Pharmacodynamic properties

The MAH includes a reference to paediatric studies and deleted the text regarding the "conditional approval".

Paediatric population
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).

~~This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited.~~
~~The European Medicines Agency will review new information on the product every year and this SmPC will be updated as necessary.~~

CHMP's comment:
The PDCO provided an opinion, including a deferral and a waiver for Cayston, (EMEA-000827-PIP01-09 on 29 October 2010). Inclusion of the proposed text is agreed.

As the MAH has fulfilled all specific obligations, the CHMP is of the opinion that the conditional marketing authorisation can be converted in a marketing authorisation not subject to specific obligation. The proposed deletion in section 5.1 of SmPC is agreed.

Patient leaflet

The MAH updated the leaflet with country specific local representatives. No other changes were deemed necessary apart from removal of sentence related to conditional MA approval.

CHMP's comment: The proposed changes are accepted.

Labelling

No changes were deemed necessary.

CHMP's comment: Agreed

3.4.2. General Conditions for the Marketing Authorisation

Annex II.B - Conditions:

The MAH will continue to submit 6 monthly PSURs (for the next two years).

Annex II.C - Specific Obligations:

As the CHMP concluded that the MAH has fulfilled all Specific Obligations, Annex II.C was updated and the list of outstanding obligations deleted.

3.4.3. Changes to Annex A

None

3.5. Follow-up measures to be fulfilled by the MAH

The MAH agreed to submit the follow-up measures as listed below, as requested by the CHMP:

Area[1]	**Description**	**Due date**[2]
Quality	**FUM 5**: The applicant will either tighten the prefiltration bioburden limit or submit the bioburden data from drug product manufacturers proposed for an additional 10 lots of commercial manufacturing experience.	30/06/2011
Quality	**FUM 6**: The applicant commits to validating the manufacturing process at the proposed manufacturing sites as outlined in Module 3, Section 3.2.R.1-1, 'Process validation scheme for the manufacture of aztreonam lysine powder for inhalation' prior to commercialization.	30/06/2011

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

4. Overall conclusion and benefit/risk assessment

Benefit

For a more definitive conclusion of the benefit of Cayston in comparison with a standard comparator in the same target group (including paediatric patients) the assessment of the responses for study GS-US-205-0110 recently became available (study GS-US-205-0110 assessment reports adopted by CHMP, Annexes 4-6).

Study GS-US-205-0110 has shown that based on the submitted efficacy (and safety data) in tobramycin experienced CF patients with chronic PA infection, aztreonam lysine provides significant lung function improvement during treatment compared to continuation of Tobi (TNS- Tobramycin nebuliser solution) with additional significant effects of decreased need of additional antibiotic treatment and hospitalization and non-inferiority during off-treatment periods including at the 6 months evaluation point.

Risk

The overall adverse events profile for Cayston in CF patients with the approved indication at the recommended dose in the present overall analysis was not different from that reported in the original Marketing Authorisation Application. Study GS-US-205-0110 AZLI did not reveal new or unexpected safety issues. However, in study GS-US-205-0110, an emerging trend was noted of increased resistance of Pseudomonas aeruginosa isolates to aztreonam and to other beta lactams.

Regarding hemoptysis, the MAH's conclusion and proposal of a targeted questionnaire are agreed. Although hemoptysis itself may not be drug related, there is the potential for exacerbation of hemoptysis due to the cough or bronchospasm associated with inhaled therapies like AZLI. This is recognised in the AZLI EU Risk Management Plan (RMP): bronchospasm in patients with severe lung disease is cited as an important identified risk. The MAH's commitment to continue closely monitor cases of hemoptysis is noted.

No SmPC safety amendments are warranted at this moment provided the MAH will continue monitoring (in PSUR):

- Hemoptysis
- Bronchospasm in Patients with Severe Lung Disease
- Immune System disorders – Hypersensitivity.
- Severe allergic reactions.
- Reports of the use of AZLI during pregnancy/lactation

Benefit / Risk Conclusion

Discussion on B/R

Study GS-US-205-0110 presents a significant contribution in confirming the positive benefit risk ratio of Cayston (AZLI) within the context of the conditionally approved indication in adult cystic fibrosis patients with chronic Pseudomonas aeruginosa (PA) infection of the lungs. In this open-label non-inferiority study of AZLI versus TNS, Cayston demonstrated favourable efficacy as judged by the improvement of the lung function parameter FEV1% predicted across 3 treatment courses of 28 days in adult tobramycin-experienced patients during treatment periods. Also for the required six months evaluation period in CF, Cayston showed non-inferiority in the primary endpoint. In addition, Cayston showed a favourable effect in prolonging time to need for IV anti-PA antibiotics for a respiratory event, total number of respiratory hospitalizations and total number of respiratory events requiring the use of IV or inhaled anti-PA antibiotics during the 6-month study period. In the small subgroup of CF patients who were tobramycin-naïve, lung function at day 28 and week 20 was better with TNS compared to AZLI although not significantly due to the small sample size, but also these patients required more additional anti-pseudomonal antibiotic treatment and admissions than AZLI-treated patients. An increase in PA isolates with decreased susceptibility and resistance to aztreonam, more frequent isolation of S.aureus in AZLI-treated subjects and appearance of cross-resistance to beta-lactam antibiotics is noted. This has the potential to impact on future treatment strategies in these patients. However, the increase in aztreonam MIC and appearance of cross-resistance in AZLI-treated patients did not result in a decrease of the favourable efficacy of AZLI in improvement of lung function in those patients during the 6 month study period.

Good monitoring of the emergence of PA resistance to aztreonam after AZLI treatment and the anticipation of the consequences for the treatment of systemic infections warrants future inclusion of appropriate information in section 4.4 and 5.1 of the SmPC, because:

- the initiation of AZLI in chronic PA infection will increase the number of PA strains with increased Aztreonam MIC > 8 and resistance to beta lactam antibiotics.
- an increase in isolation rates of other bacterial microorganisms, especially *S.aureus*, could be associated with AZLI.

Conclusion

The presently expanded efficacy and safety database does not change the favourable benefit/risk ratio for Cayston at the recommended dose in the approved indication for the suppressive therapy of chronic pulmonary infections due to P. aeruginosa in patients with cystic fibrosis aged 18 years and older.

The recently available assessment of the completed open-label, randomised, Phase 3 study, GS-US-205-0110 reconfirmed the favourable benefit/risk.

The Marketing Authorisation Holder has provided a revised draft letter of undertaking addressing the timeframes for the submission of FUM 5 and 6.

As the applicant has fulfilled all specific obligations, the CHMP is of the opinion that the conditional marketing authorisation can be converted in a marketing authorisation not subject to specific obligation.

The MAH should continue to submit 6 monthly PSURs (for the next two years).

5. Outcome of the conditional renewal procedure

Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated.

In addition, the CHMP concludes that all Specific Obligations as laid down in Annex II.C to the Opinion of the last Renewal are fulfilled and therefore recommends that a Marketing Authorisation not "subject to specific obligations" be granted.

The opinion requires amendments to the terms of the Community Marketing Authorisation.

The following annexes have been amended: Annexes I, II and IIIB.