European Medicines Agency
Evaluation of Medicines for Human Use

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FINAL ASSESSMENT REPORT

FOR

Cayston

International Nonproprietary Name: aztreonam

Procedure No. EMEA/H/C/000996

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Gilead Sciences International Ltd. submitted on 7 March 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for aztreonam lysine (AZLI), which was designated as an orphan medicinal product EU/3/04/204 on 21 June 2004. Aztreonam lysine (inhalation use) received orphan designation, for treatment of gram negative bacterial lung infection in CF. The sponsorship was transferred from MoRa Pharm GmbH to PAREXEL International Limited, United Kingdom, in July 2005 and subsequently to Gilead Sciences International Ltd, United Kingdom, in May 2007.

The calculated prevalence of this condition was 13 per 100,000 EU population.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant applied for Conditional Marketing Authorization for AZLI Article 3(1) of Regulation (EC) No 726/2004 Article 4 of Commission Regulation (EC) 507/2006.

The applicant requested the following indication: "To improve pulmonary function and respiratory symptoms for the management of CF patients aged 6 years and older with *Pseudomonas aeruginosa"*.

Protocol Assistance:
The applicant received Protocol Assistance from the CHMP on 14 October 2005. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status:
A new application was filed in the following countries: United States, Canada, Australia, Switzerland and Turkey.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Barbara van Zwieten-Boot
Co-Rapporteur: Patrick Salmon

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 7 March 2008.
- The procedure started on 26 March 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2008.
- During the meeting on 24 July 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2008.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 October 2008.
- During the CHMP meeting on 20 November 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 16 January 2009

- The Rapporteur's circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 February 2009.
- During the CHMP meeting on 17 February 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The Rapporteur's circulated an updated Joint Assessment Report to the applicant's Post Oral Hearing on to all CHMP members on 12 March 2009.
- During the meeting on 16-19 March 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion by majority votes for granting a conditional Marketing Authorisation to Cayston on 19 March 2009.

1.3 Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Pierre Demolis
CoRapporteur: Pieter Neels

- The applicant submitted written notice to the EMEA on 26 March 2009 to request a re-examination of the CHMP negative opinion for Cayston of 19 March 2009.
- During its meeting on 20-23 April 2009, the CHMP appointed Pierre Demolis as Rapporteur and Pieter Neels as Co-Rapporteur for the re-examination procedure.
- The detailed grounds for the re-examination request were submitted by the applicant on 27 April 2009. The re-examination procedure started on 28 April 2009.
- The Rapporteur's Assessment Report on the detailed grounds for the re-examination was circulated on 2 June 2009. The Co-Rapporteur's Assessment Report on the detailed grounds for the re-examination was circulated on 1 June 2009.
- The Rapporteurs' Joint Assessment Report on the detailed grounds for the re-examination was circulated on 10 June 2009.
- During a meeting of the CHMP Scientific Advisory Group on Anti-infectives (SAG-Anti-infectives) on 16 June 2009, experts were convened to address questions raised by the CHMP. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to the CHMP.
- During the CHMP meeting on 22-25 June 2009, the grounds for refusal were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22-25 June 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final positive Opinion by majority votes for granting a conditional Marketing Authorisation to Cayston on 25 June 2009. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 24 June 2009.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 21 September 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Cystic fibrosis is an autosomal recessive disorder caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that acts as a chloride channel. Disruption of the sodium and chloride ion transport mechanism of epithelial cells, associated with water transport abnormalities results in abnormally viscous secretions in different exocrine tissues, mainly the respiratory tract, pancreas, gastrointestinal tract and exocrine *g*lands. In Europe approximately 25,000 people are affected by CF.

In the respiratory tract the disorder results in progressive, obstructive pulmonary disease. The abnormally viscous mucus interferes with the mucociliary transport mechanism normally responsible for clearance of bacteria and other organisms from the airways. This makes CF patients particularly susceptible to pulmonary infections caused by bacterial pathogens such as *P. aeruginosa*, as well as *Burkholderia cepacia,* and *Stenotrophomonas maltophilia*. *Pseudomonas* infections are usually established in the first decade of life. Patients infected with *P. aeruginosa* experience episodes of acute pulmonary exacerbation, characterized by worsening respiratory symptoms and acute decline in lung function. The repeated episodes of infection and associated inflammation cause progressive damage of the lungs; *P. aeruginosa* is rarely eradicated. This chronic infection is associated with reduced life expectancy.

The current management of the pulmonary infections in CF patients is comprised of early treatment with a variety of therapies in an effort to prevent exacerbations or management without hospitalisation. It includes in addition to antibiotics a variety of therapies such as bronchodilators, mucolytic and anti-inflammatory agents and airway clearance techniques.

Intravenous antibiotic treatment, usually given for 2 weeks, is the standard therapy for pulmonary exacerbations in patients with chronic lung infection by *P. aeruginosa*. There are two main treatment strategies that are widely used for the management of chronic *P. aeruginosa* lung infection in people with CF: The first approach is giving r*egular courses* of intravenous antibiotics or inhalational antibiotics; the second approach is "*on demand*" i.e, prompt treatment of acute exacerbations as determined by clinical or radiological findings or deterioration in lung function parameters.
There is insufficient evidence to determine whether regular maintenance antibiotic treatment was more effective than treatment "on demand" in maintaining lung function in CF patients based on the limited number of randomised comparisons (and studied patients)[1]. In both cases IV therapy was the mainstay in the; patients could receive concomitant treatments such as nebulised antibiotics (25-40%)[2], oral anti-staphylococcal antibiotics and regular inhaled bronchodilators in a balanced fashion. "On demand treatment" does not seem to result in significant reduction in number of courses of treatment when compared to regular treatment.

Chronic suppressive treatment with inhalational antibiotics, in particular tobramycin nebuliser solution [TNS, TOBI, approved in the EU via the Mutual Recognition procedure in recent years] belongs now to the standard therapy in the management of CF patients with chronic pulmonary infection due to *P. aeruginosa*. The recommended dose of TOBI is 300mg twice daily (morning and evening) for 28 days. After 28 days of therapy, patients must stop treatment for the next 28 days; the rationale for intermittent dosing is to reduce the potential for antimicrobial resistance caused by continuous exposure to drug. IV antibiotics are usually reserved for the treatment of acute exacerbations or infections that fail to respond to combined oral and nebulized treatment. As a result of progress in CF

[1] Breen L, Aswani N. Elective versus symptomatic intravenous antibiotic therapy for cystic fibrosis. Cochrane Database Syst Rev 2009;4:CD002767, doi:10.1002/14651858.

[2] Elborn JS, Prescott RJ, Stack BHR,GoodchildMC, Bates J, Pantin C, et al.Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonas infection of the lungs. *Thorax* 2000;**55**(5):355–8.

care, the demographics of the CF population have evolved. The mean age of CF patients has increased to 17 years in the EU[3]. However, chronic treatment with antibiotics including inhalational tobramycin and systemic beta-lactams is associated with increased risk of resistance development[4]. Additional options for inhalational antibiotics in the target population are needed.

Aztreonam belongs to a different antibiotic class than tobramycin, the mechanism of action of aztreonam is unlike that of the aminoglycosides, and does not appear to contribute to the emergence of aminoglycoside-resistant organisms. Intravenous therapy with aztreonam has also been used in the treatment of acute infectious exacerbations in CF patients; however, the reported trials were rather small. Moreover, aztreonam has activity against aminoglycoside-resistant *PA*. Aztreonam is highly active against most aerobic gram-negative bacteria including *Pseudomonas* species; it has no useful use against gram-positive infections. Aztreonam activity is not significantly inhibited by sputum in the CF lung. By comparison, the activity of aminoglycosides is known to be antagonized by sputum.

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.

The CTD includes a review of published literature relevant to the pharmacology, pharmacokinetics, and toxicology of aztreonam.

The originally sought therapeutic *indication* for Aztreonam Lysine 75 mg powder and solvent for nebulizer was "Cayston is indicated to improve pulmonary function and respiratory symptoms for the management of CF patients aged 6 years and older with *Pseudomonas aeruginosa*".

The revised sought indication is:

"A 28-day course of Cayston is indicated for the treatment of chronic airway infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 18 years and older to improve pulmonary function and respiratory symptoms."

The primary support for this indication is based on two single courses, placebo-controlled studies; a multiple course, comparative, active controlled study is ongoing.

During the oral hearing, the applicant presented the view that proposed 28-day indication for AZLI would be consistent with the "on-demand" treatment paradigm. According to the applicant, "On-demand" options include IV aminoglycosides and beta-lactams in 2-4 week treatments; 28-day course

[3] European Cystic Fibrosis Society, Kerem E, et al. The European Cystic Fibrosis Registry Report on 2003 Data, Summary, 2006: 2 p.
[4] C A. Merlo et al. *Chest*. 2007; 132:562-568. Incidence and Risk Factors for Multiple Antibiotic-Resistant *Pseudomonas aeruginosa* in Cystic Fibrosis

of TNS also commonly being employed. PO ciprofloxacin in 2-3 week treatments is marginally effective. 3% absolute improvement FEV1 is considered clinically important.
The applicant claimed that patients in the provided pivotal studies were tested in a setting according to the "on demand" treatment strategy and the observed results were clinically important. However, the CHMP questioned this claim (see inclusion criteria and benefit-risk discussion).

The *recommended dosage* regimen is subsequently changed from both adults and paediatric patients 6 years of age and older to adults only.
One reconstituted single-use vial administered (by inhalation over a 2 to 3 minute period) three times daily using the Altera nebuliser for a 28-day course.

Furthermore, the following additional changes are included;

"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, at least a 28 day off period between courses is recommended.

Paediatric population

Cayston is not recommended for use in children and adolescents (i.e. patients < 18 years) as the safety and efficacy of the drug has not been fully established in this patient population".

Cayston is only for inhalation use and not for oral, intravenous, subcutaneous, intramuscular, or intrathecal use.

2.2 Quality aspects

Introduction

Cayston is presented as powder and solvent for nebuliser solution containing 75 mg of aztreonam as active substance. For the lyophilised powder the ingredients are lysine monohydrate, water for injection and for the saline solution 0.17% sodium chloride and water for injection.
The active substance is lyophilized and must be reconstituted with sterile saline (0.17% sodium chloride) diluent to adjust osmolality prior to inhalation. The reconstituted solution has to be administered with a specific device, a Nebuliser Handset and aerosol head connected to an eFlow control unit. The device is not part of the medicinal product and needs to be provided separately.
The primary container for the dry powder consists of sterile, depyrogenated, 2 ml type I amber glass vial and a siliconised gray butyl lyophilisation stopper with a piece tear-off seal. The primary container for the diluent consists of a blow/fill/seal container that is formed of low density polyethylene (LDPE) as part of the filling process. The container closure system is formed as part of the aseptic packaging process, resulting in a sterile ampoule that is sealed by fusion.

Active Substance

The active substance is aztreonam its chemical name is (*Z*)-2-[[[(2-amino-4-thiazolyl)[[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino]oxy]-2-methylpropionic acid according to the IUPAC nomenclature.
Aztreonam contains two chiral centres at the C-2 and C-3 positions of the β-lactam ring, and an oximino in the Z-configuration. Aztreonam is produced as the 2S,3S-enantiomer.
The active substance is white to off-white crystalline powder. In fact four polymorphs of aztreonam are known (form α, β, δ, and γ) with different X-ray diffraction patterns and IR spectrum. The β polymorph is described in the USP Pharmacopeia. The active substance is soluble in dimethylformamide, dimethylsulfoxide, in buffered aqueous solutions; slightly soluble in ethanol; slightly soluble in water and methanol and practically insoluble in toluene, chloroform, dichloromethane and ethyl acetate.

Manufacture

Aztreonam is synthesised in three reactions steps following purification by re-crystallisation. The manufacturing process has been adequately described. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented.
Structure elucidation has been performed by mass spectroscopy, UV spectroscopy, ^{1}H-NMR spectroscopy and ^{13}C-NMR spectroscopy. The molecular weight was determined by elemental analysis which is in agreement with the expected molecular weight. The Polymorphic form is elucidated using X-ray diffraction and IR spectra analysis.

- **Specification**

The active substance specifications include tests for appearance (white to off-white crystalline powder), identification (IR), optical rotation (Ph. Eur.), water content (Ph.Eur), assay (HPLC), impurities (HPLC), heavy metals (Ph.Eur), residue on ignition (Ph.Eur), organic volatile impurities (GC), microbial limits (Ph. Eur.) and bacterial endotoxin (Ph. Eur.).
It was verified that all specifications reflect the relevant quality attributes of the active substance. The non-pharmacopoeia analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines. It was noticed that further validation and information regarding some analytical methods are needed and it was agreed that this information can be provided as a quality commitment.
Impurities were described, classified as process related impurities and possible degradation products, and qualified. Nevertheless, the Applicant must provide further information regarding impurities in the active substance.
Residual solvents were controlled in the active substance. However, further information regarding the residual solvents in the active substance is needed, in order to confirm that the limits are according to the relevant ICH requirements.
Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The active substance is intended for storage in a refrigerator. The stability results from long-term (5 °C ± 3°C) and accelerated studies (25°C ± 2°C/60% RH ± 5% RH) were completed according to ICH guidelines demonstrated adequate stability of the active substance. During the stability studies the following parameters were controlled: appearance, purity, impurities, bacterial endotoxins and water content. It was noticed that the test methods applied are those used for release of the drug substance. The active substance remained within the specifications for up to 24 months after long term storage at -20°C and 5°C.
Furthermore stress studies were also performed under acid, base, light, heat and oxidation conditions. It was noted that 5% of degradation of the active substance when stored under light, heat and oxidation conditions. The photostability study that was performed in accordance with the note for guidance on photostability testing of new active substances and medicinal products (CPMP/ICH/279/95) confirmed that the active substance is photosensitive. Based on the stability results it was concluded that the proposed re-test period is justified when the active substance is stored in the original packing material and protect from light and elevate temperatures.

Medicinal Product

<u>Dry Powder</u>

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified. Furthermore, all the excipients used are well known and commonly used in the pharmaceutical industry.
A summary of the development of the drug product has been provided taking into consideration the proposed route of administration and usage. The quantitative ratio of lysine to aztreonam is unchanged between clinical trials Phases I to III and the proposed commercial formulation.
It was confirmed that the formulation and manufacturing process proposed for the commercial formulation and manufacturing process is identical to that used to prepare primary stability and clinical batches. No significant differences in manufacturing approach and key processing parameters are apparent between sites, or between batch sizes. It was verified that the source of the active substance will not have an impact in manufacturability and physicochemical properties of the finished product.
The Altera nebulizer generates an aerosol by pumping solution through a perforated vibrating membrane.
Dry Powder aztreonam lysine is packaged with the solvent (water containing 0.17% w/v sodium chloride) and is reconstituted to form a solution for nebulisation.

- **Adventitious Agents**

Neither the excipients nor the active substance is derived from human or animal origin. Certificates of the manufacture of L-lysine monohydrate confirmed that no materials of animal origin, nor milk or milk derivative, are used in the manufacture of L-lysine monohydrate.

- **Manufacture of the Product**

The manufacturing process is a standard process for this kind of formulation and consists of the following steps: Preparation of AZLI solution (lysine monohydrate and aztreonam), filtration, filing, lyophilization, sealing and packaging.
The equipment used is commonly available in the pharmaceutical industry. It was verified that the critical steps of this manufacturing site have been identified and characterised. The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.
Furthermore, validation data on the manufacture process at both proposed manufacturing sites should be provided before to commercialisation.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance, identification with IR and HPLC, reconstitution, water content, assay, impurities in the finished product were described, classified as process related impurities and possible degradation products, and specified. It is important to underline that further information regarding some impurities in the finished product must be provided.
All analytical procedures that were used for testing the medicinal product were properly described. Furthermore, all relevant analytical methods were satisfactorily validated in accordance with the relevant ICH guidelines.
All analytical procedures that were used for testing the finished product were properly described. It was noted that further information regarding some analytical methods will be provided. All relevant methods were validated in accordance with the relevant ICH guidelines. Nevertheless, the applicant committed to provide further information regarding the validation of some analytical methods.
The batch analysis data for sixteen batches confirm that the lyophilised powder can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the finished product.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Five scale batches have been stored at long term (5 °C ± 3°C) and four scale batches have been stored at accelerated conditions

(25°C ± 2°C/60% RH ± 5% RH). All batches were packed in the proposed market packaging. It was verified that the following parameters were controlled: appearance, reconstituted solution, assay, degradation product content, lysine content, water content, pH, osmolality, particulate matter, sterility and bacterial endotoxins. It was noted that some additional analytical methods to release testing have been used (i.e osmolality, particulate matter, bacterial endotoxins and lysine content). All attributes of the finished product remained within the acceptance limits of the specification after 24 months of long-term storage and 6 months storage under accelerated conditions.
The results of the photostability study, which was conducted under ICH conditions, demonstrated that the finished product when stored in the primary container closure system showed no change in physicochemical properties upon exposure to light. Stress studies under high temperatures show that that no changes in physicochemical properties and a slight increase in the degradation products.
No significant changes in physicochemical properties were observed when lysophilised powder was reconstituted and stored at room temperature for up to 12 hours following long-term storage at 5 °C. Furthermore, the data indicate that the reconstituted solution should not be stored for more than 12 hours prior to use at 25°C.
The current 24 month real time long term stability data and accelerated stability data for 6 months support the proposed shelf life and storage condition of 'Store in a refrigerator at 2-8^{o}C' for a shelf life of 2 years. Furthermore, the lyophilised powder can be transported and stored by the patient for 8 weeks below 25^{o}C. The reconstituted solution of aztreonam lysine may be stored below 25^{o}C for 12 hours before use.

Saline Solution 0.17% Diluent

- **Pharmaceutical Development**

The diluent is a single use, sterile 1 ml preservative-free 0.17%w/v sodium chloride solution in a blow fill seal ampoule co-packaged with the drug product. It is important to underline that there is no active substance in the diluent. The above concentration of sodium chloride solution was selected to provide a minimum permanent anion concentration while ensuring that the osmolality of the final reconstituted solution does not exceed 550 mOsm/kg which would contribute to bronchospasm and coughing.
The aim during development was to obtain a diluent which was suitable for reconstitution of the lyophilised powder and where the final solution would demonstrate physicochemical characteristics appropriate for patient administration by nebulisation.
The diluent pH was not considered significant as it is the aztreonam lysine (lyophilised powder) which contributes mainly to the final pH of the finished product solution, and the diluent has no significant buffering capacity. The osmolality of the final reconstituted solution was controlled by including a low amount of sodium chloride. Stability studies of reconstituted solutions of lyophilised powder with the diluent demonstrated compatibility of the diluent with the finished product.
It can be concluded that all information regarding the choice of the excipients, which are commonly used in the pharmaceutical industry, are sufficiently justified.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as preparation of a sodium chloride solution, mixing, sterile filtration, filling into individual blow/fill/seal ampoules and packaging.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was noticed that the critical steps have been identified and controlled. Validation studies for the filters used in the manufactured of the diluent were performed to demonstrate the ability of the filters to retain microbes and also demonstrated compatibility of the filter materials with the sodium chloride solution.
The manufacturing process has been adequately validated and the results of the manufacturing validation reports were considered satisfactory.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The diluent specifications were established according the ICH guidelines and include the following tests: appearance, identification tests for sodium (Ph.Eur.) and chloride (Ph.Eur.), assay, sterility, endotoxin and deliverable volume.
Two non-compendial methods (appearance and deliverable volume of diluent) that were used for testing the diluent were properly described. No further validation was needed since the analytical methods are carried out according to pharmacopoeial methods.
The batch analysis data for nine pilot scale batches confirm that the diluent can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the diluent.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Four scale batches have been stored at long term at (5 °C ± 3°C and 25°C ± 2°C/60% RH ± 5% RH) and at accelerated conditions (40°C ± 2°C/60% RH ± 5% RH). All batches were packed in the proposed market packaging. It was verified that the following parameters were controlled: appearance, assay for sodium chloride, weight loss, pH, fill volume, sterility and bacterial endotoxins. Two stress stability studies were conducted on each of three primary stability batches. In one study the diluent was subjected to four temperature cycles, with each cycle consisting of 24 hours at 5 °C at 24 hours at 25 °C. In a second study, the diluent was subjected to four freeze thaw cycles, with each cycle consisting of 24 hours at -20 °C at 24 hours at 25 °C. Based on the data obtained for long term, accelerated and stress studies it can be concluded that the diluent does not require any special storage conditions.

Discussion on chemical and pharmaceutical aspects

Information on development, manufacture, control of the active substance and the finished product have been presented and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product.

2.3 Non-clinical aspects

Introduction
In support of the application, Gilead Sciences have provided a literature review that describes the mechanism of action and activity of aztreonam against a range of bacteria as well as pharmacokinetic and toxicology given its extensive clinical experience of over 20 years. The non-clinical testing performed for aztreonam primarily focuses on local and systemic effects resulting from inhalation exposure. Additionally, studies examining dermal and ocular irritation as well as the allergenic potential of AZLI were also conducted. Moreover, a study comparing the pharmacokinetic profiles of the approved formulations of aztreonam and AZLI was also performed.

All pivotal pharmacokinetic, toxicology and local tolerance studies were stated as performed to GLP criteria.

Pharmacology
Aztreonam acts like beta-lactam antibiotics through interference with bacterial cell wall biosynthesis. It has high affinity to PBP3 of gram-negative bacteria.

Aztreonam has been in use (via the parenteral route) for several decades and it is known that it is active against gram-negative bacteria including *Pseudomonas aeruginosa*. Recent *in vitro* data from Europe are however limited. Also, data from multidrug resistant organisms are very limited. One recent European study showed a wide range of MIC values (0.125 – 512 µg/ml). A limited *in vitro* study comparing MICs of aztreonam lysinate to aztreonam arginate showed no relevant difference between these two salts.

Aztreonam was active against *Pseudomonas aeruginosa* in a protection study in mice, in meningitis models in rats (*Haemophilus influenzae*) and rabbits (*Pseudomonas aeruginosa*) and in a pneumonia

model (*Pseudomonas aeruginosa*) in guinea pigs. Also these *in vivo* data were limited: the publications were approximately 20 years old, they provided no evidence of complete eradication of the infection, and there were no data from experiments by which the compound was given by inhalation. Hence, the provided animal experiments do not provide relevant evidence that aztreonam administered via inhalation is effective against *Pseudomonas aeruginosa* in the respiratory system. Clinical studies will therefore have to provide this evidence.

Data regarding resistance show a decreased susceptibility, especially in Europe. Limited data on multidrug resistant isolates show that susceptibility in these isolates was low (10-20%). In the development of resistance, likely more mechanisms are involved. Aztreonam seems stable to metallo-beta-lactamases (class B) and OXA beta-lactamases (class D). Regarding class C beta-lactamases, aztreonam is at least susceptible to hydrolysation by AmpC. Two common beta-lactamases from class A (TEM- and SHV-type beta-lactamases) have only rarely been reported in *Pseudomonas aeruginosa***.** Several other class A type beta-lactamases have been reported to hydrolyse aztreonam.

Based on parenteral use, as for all beta-lactam antibiotics, for aztreonam, time above MIC is the PK/PD parameter best correlating with efficacy. However, for the current indication, local concentrations in the lung are important. No data were provided regarding concentrations that may be expected to occur in the lungs, neither was it discussed by the applicant whether local concentrations are expected to be high enough, also when compared to high MICs (MIC90 of >512 µg/ml is highest reported MIC90 in recent European study).

No information was provided regarding secondary pharmacodynamics. This is endorsed. As a beta-lactam antibiotic aztreonam is a member of a well-known class.

A safety pharmacology study in conscious dogs is planned by the applicant to evaluate the CV/respiratory effects of aztreonam. The results of this study are anticipated to be complete during 1Q2009 and will be submitted to the CHMP as soon as the report becomes available.

In vitro, aztreonam showed evidence of at least some synergy with a wide range of antibiotics. No noteworthy antagonism was observed. No discussion was provided regarding interactions which may be expected with agents that are specifically used by CF patients.

Although provided data on *in vitro* susceptibility of aztreonam were rather limited, it gives a picture of an agent which is active against *Pseudomonas aeruginosa*, but with decreasing susceptibility, especially in Europe. Further information regarding susceptibility will have to appear from the clinical data. Lacking is a discussion regarding expected local exposure in association with MIC values.

Pharmacokinetics

The pharmacokinetics of aztreonam was based on literature data for aztreonam arginine and studies performed by the applicant with aztreonam lysine and aztreonam arginine. In the provided literature for aztreonam arginine, the analysis of aztreonam was performed using HPLC UV, thin-layer radio-chromatography and scintillation counting. The current studies were performed using LC-MS as analysis method. In summary, inhalation of aztreonam lysine in rats and dogs following a single dose results in rapid absorption with T_{max} occurring at the completion of the inhalation exposure or within minutes thereafter. In rats, parameters indicative of systemic exposure (C_{max} and AUC) tended to increase in relationship to dose whereas there was considerable variability in clearance (CL/F) and volume of distribution (Vd/F). Estimates of plasma ranged from 0.87 to 1.67 h and results indicate that steady state was reached within the first day of dosing. In dogs, parameters indicative of systemic exposure did not exhibit consistent trends but an overall increase was generally observed as dose increased. No consistent trends were identified in estimates of clearance or volume of distribution. The T½el values for dogs exposed via inhalation appeared to be higher than values from rats. No major differences between males and females occurred with either species.

The plasma protein binding of aztreonam (administered as arginine salt) ranged from 67% in mouse, 60% in rat, 28-34% in dogs, 49-59% in monkeys and 27% human serum. Tissue distribution studies of

aztreonam arginine were performed in mice, rats, rabbits, dogs, and Cynomolgus monkeys following intramuscular and subcutaneous administration (Kita et al., 1986; Singhvi et al., 1984; Bonner et al., 1981). It seems that based on the data for arginine after intramuscular administration that the kidney, liver, meninges and pancreas are target organs. Placental transfer of aztreonam occurs in pregnant rats and aztreonam is present in the milk of dams.

The applicant has shown that aztreonam is stable or metabolized slowly by the indicated CYP450 isoenzymes and FMO enzymes. Aztreonam also appeared to be stable in pulmonary S9 fractions, hepatic and pulmonary microsomal fractions and cryopreserved hepatocytes from normal healthy human donors as well as rats, dogs, and cynomolgus monkeys. This suggests that drug-drug interactions via CYP induction or inhibition are unlikely.

In the study by Kripalani *et al.* (1984) thin-layer radio-chromatography and HPLC-UV were used to identify the metabolites in urine after administration of aztreonam arginine in rats. They identified a major metabolite SQ26,992 and 4 unknown metabolites. In healthy human subjects, the urinary excretion of unchanged aztreonam accounted for 66-68% of an intravenous or intramuscular dose ranging from 125 to 4000 mg. Kripalani et al. (1984) provided an overview of the excretion of unchanged aztreonam and its metabolites in rat, dog, monkey and human after administration of aztreonam arginine which indicated that aztreonam is mainly excreted via urine and 2-10% of the urinary metabolites remained unidentified.

In a study by Kripalani *et al*. (1984), the excretion of aztreonam arginine was investigated in rat, dog and monkey. Excretion in rat was ~70% in urine and ~30% in faeces. In dog, ~88% of the subcutaneous dose was excreted via urine and faecal excretion averaged ~10%. In monkeys excretion via urine accounted for ~42% and excretion in faeces also accounted for ~42%. In humans, urinary excretion is the primary mode of elimination.

The *in vivo* inhibitory effect is only observed at high dose levels (40 to 300 mg/kg/day) given aztreonam arginine intravenously over a four week period to monkeys and the applicant stated that it would not be expected to occur at the maximum clinically intended inhaled dose of 4.5 mg/kg/day in humans. In clinical studies, aztreonam showed no significant interactions with cephradrine, clindamycin, gentamicin, metronidazole or nafcillin when administered to healthy male volunteers as single-dose infusions in a three-way balanced crossover study. Several of these drugs are cleared renally, while some, such as clindamycin, appear to have a component of clearance due to oxidative metabolism mediated by CYP3A4. No formal drug interaction studies have been performed with aztreonam. However, aztreonam was not shown to significantly inhibit the major human drug metabolizing cytochrome P450 enzymes at clinically relevant doses and so was considered to be an unlikely inhibitor of these enzymes *in vivo*. Moreover, aztreonam did not significantly induce human drug metabolizing enzymes and transporters through activation of AhR or PXR and so is not thought to cause clinically relevant drug-drug interactions through AhR or PXR.

Toxicology

Nonclinical toxicology of AZLI associated with inhalation exposure was characterised by an acute single-dose inhalation study in dogs, a 7-day repeat-dose inhalation study in rats, pivotal 28- and 90-day repeat-dose inhalation studies in rats and dogs, and a 104-week repeat-dose inhalation carcinogenicity study in rats. Local tolerance studies to examine potential dermal and ocular irritation and allergenicity studies were performed in rabbits and guinea pigs, respectively.

- Single dose toxicity

Sixteen male and 16 female beagle dogs (~4.5-6.5 months old) were exposed to AZLI (0 mg aztreonam/kg – vehicle control, 50 mg aztreonam/kg – low dose, 100 mg aztreonam/kg – intermediate dose and 200 mg aztreonam/kg – high dose) using a closed face-mask system with the dogs breathing passively from a DeVilbiss ultrasonic nebuliser for 15, 30 and 60 minutes. The high dose was the maximum attainable dose as determined by aerosol characterization investigations using a clinically relevant formulation (100 mg aztreonam/ml). General clinical condition and health was observed

before exposure, during exposure and approximately 1 to 2 hours after exposure. Blood and urine samples were taken for haematology, coagulation, clinical chemistry and urinalysis examinations. Single-dose blood and urine toxicokinetics were also recorded.

Estimated mean achieved doses were 0, 44.2, 107.8 and 169.2 mg/kg for groups 1, 2, 3 and 4, respectively. There were no adverse clinical signs or treatment-related effects observed on body weight, food consumption, blood biochemistry, urinalysis, necropsy, organ weight or histopathology. The NOEL was considered to be 169.2 mg/kg.

Single-dose pharmacokinetic parameters are summarised in Table 1, while aztreonam was detected in the urine in all treated animals with a mean amount excreted over a 24-hour collection period of 20.0, 32.5 and 61.0 mg for groups 2, 3 and 4, respectively.

Table 1. Mean (SD) Toxicokinetic Values in Beagle Dogs Following a Single Dose of AZLI by Inhalation

Treatment Group	Achieved Dose (mg Aztreonam/kg)	Tmax[a] (hr)	Cmax (μg/ml)	AUC $_{(0-\infty)}$ (μg-hr/ml)	AUC $_{(0-t)}$ (μg-hr/ml)	T½el (hr)
2 (Low dose)	44.2	0.75 (0.29)	4.62 (1.43)	12.7 (9.44)	12.6 (7.38)	5.78 (1.24)
3 (Intermediate dose)	107.8	1.25 (0.50)	5.41 (2.39)	19.5 (9.52)	19.2 (9.43)	6.15 (2.11)
4 (High dose)	169.2	0.813 (0.898)	12.1 (6.61)	35.8 (21.8)	35.6 (17.6)	5.31 (2.23)

[a] Approximate exposure duration: Group 2 – 15 min; Group 3 – 30 min; Group 4 – 60 min

- Repeat dose toxicity (with toxicokinetics)

7-Day Dose Range Finding Inhalation Toxicity Study of Aztreonam in Rats (Study 663632, GLP)
Male and female Sprague-Dawley rats (6/sex/group; ~11-12 weeks old) were administered target dose levels of 0, 50, or 200 mg/kg/day using aerosolized AZLI (100 mg/ml) via nose only inhalation with a Hospitak 952 airjet nebuliser. General clinical condition and health was observed before exposure, during exposure and approximately 1 to 2 hours after exposure. Blood and urine samples were taken on Days 7 and 8 of study for haematology, coagulation, clinical chemistry and urinalysis examinations. Following 7 days of treatment, animals were euthanized and subjected to detailed necropsy and organ weight analysis.

Overall group mean estimated total doses of 0, 34 and 144 mg/kg/day (estimated mean pulmonary doses of 0, 2.4 and 10.1 mg/kg/day) were achieved for Groups 1, 2 and 3, respectively. There were no observed adverse clinical signs or treatment related effects on body weights, blood biochemistry, urinalysis or necropsy findings that could be attributed to aztreonam. An increase in prostrate weight was observed for the mid (non-significant) and high dose groups (significant) but no related necropsy findings were noted in the prostrate. It was unclear whether this change was related to treatment. Based on these results doses of 35, 70 and 150 mg/kg/day were considered appropriate for the subsequent 28 day study in the same species.

28-Day Inhalation Toxicity Study of Aztreonam in Rats with a 14-Day Recovery Period (Study 663559, GLP)
Male and female Sprague-Dawley (80/sex; ~6.5-7.5 weeks old) were assigned to one of four treatment groups and were administered AZLI (low dose 35 mg/kg, intermediate dose 70 mg/kg and high dose 150 mg/kg) or vehicle control for 28 days. Reversibility of treatment-related effects were analysed in selected animals in vehicle control and high-dose treatment groups for 14 days upon completion of dosing.

28-Day Inhalation Toxicity Study (Aztreonam and Degraded Aztreonam Products) in Rats with a 14-Day Recovery Period (Study 668117, GLP)
Male and female IGS(CD) Sprague-Dawley rats (72/sex; 6-7 weeks old) were assigned to one of three treatment groups and were administered vehicle (Group 1), AZLI (Group 2), or degraded AZLI (Group 3) for 28 days. Clinical vials of AZLI were degraded at 74°C for 5 days and doses obtained

were used to establish acceptable impurity levels for the marketed product. Inhalation exposure used a nose only system with the rats breathing passively while restrained in a clear, tapered, polycarbonate tube attached to a central plenum exposure chamber that had been calibrated to deliver an aerosol generated by airjet nebulisers. Reversibility of treatment-related effects was evaluated in 5 animals per sex per group for 14 days upon completion of the main study.

90-Day Inhalation Toxicity Study of Aztreonam in Rats with a 28-Day Recovery Period (Study 664348, GLP)
Male and female Sprague-Dawley rats (104/sex; ~6-7 weeks old) were assigned to one of five treatment groups and administered AZLI (30, 60, 120 mg/kg/day – Groups 2, 3 & 4), degraded aztreonam formulation (120 mg/kg/day – Group 5) or vehicle control (Group 1) for 90 days via nose only inhalation using the Hospitak 952 airjet nebuliser. Animals (5 male and female) in the vehicle control and high dose group were held for 28 days after completion of the dosing period to evaluate reversibility of treatment-related effects.

28-Day Inhalation Toxicity Study of Aztreonam in Dogs with a 14-Day Recovery Period (Study 663496, GLP)
Male and female beagle dogs (16/sex; ~6 months old) were assigned to one of four treatment groups and administered AZLI (40, 80 and 200 mg/kg/day – groups 2, 3 & 4) or vehicle control (group 1) for 28 days. Animals (2 male and female) in the vehicle control and high dose group were held for 14 days after completion of the dosing period to evaluate reversibility of treatment-related effects.

90-Day Inhalation Toxicity Study of Aztreonam in Dogs with a 28-Day recovery Period (Study 664353, GLP)
Male and female beagle dogs (20/sex; 6 months old) were assigned to one of four treatment groups and administered AZLI (35, 70 and 140 mg/kg/day – groups 2, 3 & 4) or vehicle control (group 1) for 90 days. Animals (2 male and female) in the vehicle control and high dose group were held for 28 days after completion of the dosing period to evaluate reversibility of treatment-related effects.

In above repeat-dose toxicity studies, no significant systemic toxicities were shown. The NOAEL after 90 days exposure in rats was 32 mg/kg/day because of olfactory epithelial atrophy at 62 mg/kg/day. The NOAEL after 90 days of exposure in dogs was 133 mg/kg/day. In rat, a dose dependent mild irritancy effects in the upper respiratory tract can be shown. Both in the rat and the dog studies partly reversible irritancy effects in the upper respiratory tract are shown.

- Genotoxicity

Aztreonam was not genotoxic in a chromosome aberration assay in Chinese hamster ovary cells and in a mouse lymphoma assay scoring for forward mutations at the thymidine kinase locus in L5178Y cells.

- Carcinogenicity

A 2-year inhalation carcinogenicity study was performed with aztreonam lysine in rats. Evidence of nasal irritation was found, as was also in repeated-dose toxicity studies. In high dose, the incidence of C-cell adenomas in the thyroid gland (18%) was increased in female animals and well above the historical control incidence (7-10%). No attempt was made by the applicant to provide a possible mechanism behind this finding. There is hardly a safety margin for this effect: the safety margin based on the free fraction was 2.2 when based on AUC and 9 when based on Cmax.

No carcinogenicity study in a second species was performed. Aztreonam is an old substance by the parenteral route and from the current rat study there is no indication that aztreonam causes tumours locally in the airways. However, no attempt is made by the applicant to discuss the consequences for the paediatric population.

- Reproduction Toxicity

Literature references indicate that aztreonam has no adverse reproductive effect in rats at doses up to and including 750 mg/kg/day. Based on the dose levels achieved with aztreonam in CF patients (4.5 mg/kg/day), it is considered that aztreonam will not pose a significant risk to reproductive and/or developmental capacity of human CF patients. However, since it has been established that aztreonam crosses the placenta and enters the foetal circulation in rats and no clinical studies on reproduction in pregnant human females with CF have been performed to date, aztreonam should be used during pregnancy only if the potential benefit outweighs any potential risks.

No information was provided regarding the use in juvenile animals. This is endorsed. The exposure will be mainly pulmonary and the pulmonary system is under development up to approximately two years of age, whereas AZLI is not indicated for children of that age group.

- Local tolerance

Aztreonam lysinate was not irritating to rabbit skin and rabbit eyes.

Aztreonam-sensitized and challenged guinea pigs did not exhibit evidence of the production of reaginic antibodies which would elicit an allergic reaction.

- Other toxicity studies

The drug substance impurities E-isomer and Open Ring and the drug product impurities Lysine adduct 1 and 2, Aztreonam dimer, E-isomer and Open Ring are sufficiently qualified regarding general toxicity. These impurities are not yet qualified regarding potential genotoxicity.

Two *in vitro* genotoxicity studies as well as a structural alert analysis using DEREK are being performed and will be submitted as soon as available. If structural alert analysis shows structural alerts for genotoxicity, those impurities need to be tested at least at 250 µg/plate in the Ames test In this case, where the Ames test is not suitable, equivalent concentrations should be applied in the alternative tests that are proposed by the applicant. If structural alert analysis reveals no genotoxic alerts, the levels at which the applicant proposes the impurities to be tested, can be regarded sufficient.

Trimethylsilanol was found in the nebuliser solution (up to 3 µg/vial) when it was left to stand for more than 1 hour. Sufficient evidence was provided that no toxicity is expected from trimethylsilanol at concentrations of 3 µg/vial and that overall, trimethylsilanol can be considered non-genotoxic. An extractable/leachable study was performed with the rubber stopper of the vial. The major extractable compounds from water extraction were methylcyclopentane (maximum intake 6.3 µg/day), cyclohexane (maximum intake 3.3 µg/day), and butylated hydroxytoluene (maximum intake 3.6 µg/day). The maximum intakes of these extractables are only slightly higher than the Threshold of Toxicological Concern (1.5 µg/day, Guideline on the limits of genotoxic impurities). Given that the TTC of 1.5 µg/day is based on lifetime daily exposure and that the expected use of Aztreonam lysine will not be continuously, but for 28 days followed by a period of at least 28 days without therapy, it is not expected that these extractable compounds will give reason for concern.

Ecotoxicity/environmental risk assessment

The environmental risk assessment was completed. Based on the results of the phase II Tier A assessment, risks to the environment are assumed to be negligible.

Discussion on the non-clinical aspects

Both in rat and dog studies, no significant systemic toxicities were encountered. However, partly reversible irritancy effects in the upper respiratory tract were shown. In theory, long term chronic irritation could result in cancer (as a result of increased cell division during tissue repairment). It can be concluded that this effect is not specific to aztreonam. In dogs, this effect is not clearly present.

Furthermore the dog would have been a better animal model based in the breathing (through mouth (dog) versus nose (rat)). Also, the inhalation time for the laboratory animals is much longer (up to 4 h) than that for intended clinical use (2-3 min), which implies that local concentration in humans is probably relatively high compared with that in animals. Although effects are mild, and restricted to the upper airways, clinical relevance cannot be ruled out with certainty and a comment on possible irritancy effects in the respiratory tract of patients can be considered for the RMP.

The applicant discussed the mechanism of the C-cell adenoma and its relevance only in a very general way, but did not discuss the relevance of the observations in this particular situation. C-cell tumours are quite rare in humans, but C-cell carcinoma or medullary thyroid carcinoma do occur in humans and account for 5-10% of all thyroid cancers, of which about 25% are hereditary (Leboulleux et al, 2004). An important argument of the applicant is the bad prognosis for cystic fibrosis patients who are infected with Pseudomonas. However, life expectancy is rising up to 45 years currently. In that situation, the relevance of these tumours is becoming important. It appears from the developments hitherto and the fact that clinical studies were performed in children that the product is indeed intended to be used also in children (see also clinical AR). In conclusion, considering the increasing life expectancy especially for young patients and considering the fact that only one carcinogenicity study has been performed with aztreonam, it is still necessary to address the relevance of C-cell adenoma in this specific situation.

2.4 Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical programme overview

Completed studies

Table 2A. Clinical Study Programme (completed trials)

Study	Primary Objective of Study	Start and End Date	Study Design	Dose	Dose Duration	No. of Pts/Type	Age Range, yrs (mean)
CP-AI-001	Safety, tolerability, and PK	Nov 02 – Dec 02	Phase 1, single center, double- blind, randomized, placebo- controlled trial	95, 190 or 285 mg	Single ascending dose	24 healthy volunteers: 3 groups of 8 subjects (6 active / 2 placebo	18 to 55 (35)
CP-AI-002	Safety, tolerability, and PK	May 03 – Oct 03	Phase 1b, multicenter (8 centers), double-blind, randomized, placebo-controlled trial	75, 150 or 225 mg	Three incremental dose over three days increased every 24 hr if MTD not reached	35 adult and adolescent CF patients.	Adults: 19 to 54 (33) Adolescents: 13 to 17 (16)
CP-AI-003	Safety and efficacy	Nov 03 – Aug 04	Phase 2, multicenter (20 centers), double-blind, placebo-controlled trial	75 or 225 mg	14 days BID	105 (31 placebo, 37 AZLI 75 mg, 37 AZLI 225 mg) CF patients with lung disease due to PA	13 to 53 (26)
CP-	Safety and	Feb	Phase 3, multicenter	75 mg	28 days	211 CF patients	7 to 65 (26)

AI-005	efficacy	05 – Sept 06	(56 centers), double-blind, randomized, placebo-controlled trial		BID or TID	with lung disease due to PA (76 placebo, 69 AZLI BID an 66 AZLI TID	
CP-AI-007	Safety and efficacy	Jun 05 – Apr 07	Phase 3, multicenter (53 centers), double blind, randomized, placebo-controlled, multinational trial	75 mg	28 days TID	164 CF patients with lung disease due to PA (84 placebo, 80 AZLI TID	7 to 74 (30)

Ongoing study

Table 2B. Clinical Study Programme (ongoing trial)

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects in Safety Populationa	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	CP-AI-006	Assess long term safety of AZLI; primary endpoint – AEs, airway reactivity, vital signs, labs. Secondary disease related endpoints include FEV1 and CFQ-R. Microbiology endpoints.	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	207 at the 01 March 2007 cutoff (82 BID, 125 TID)	Patients with CF	Up to nine 28-day courses of AZLI, each course followed by 28 days off treatment	Ongoing; Interim

Comparison of trial formulations with finished product

Aztreonam is provided as a sterile, lyophilized powder that is reconstituted with a sterile saline diulent (0.17% sodium chloride) immediately prior use. The solution should be administered by the PARI eFLOW Nebuliser (subsequently named Altera).

The first eFlow to deliver aztreonam was the eFlow IMP model and was used in the Gilead Phase 1a clinical programme. The control unit and nebuliser handset for the eFlow IMP were different in appearance than later eFlow models, although the aerosol head and vibrating mesh were comparable and the aerosol characteristics were the same. The Phase 1b clinical study used the Pilot Series 2 version of the eFlow. The Phase 2 clinical study used the Pilot Series 3 version of the eFlow. The Phase 3 clinical studies used a 510(k) cleared version of the eFlow, model 78G1004.

Pharmacokinetics

To support the pharmacokinetics of Aztreonam, 5 studies have been submitted (CP-AI-001, -002, -003, -005, -007). Study -001 was the only healthy subject study, with available plasma and urine data. The other studies included CF patients, and in these only sparse data were obtained from plasma and sputum. Furthermore, literature data are provided.

Literature data indicate that aztreonam is poorly absorbed from the gastrointestinal tract and is therefore given i.v. or i.m. Absorption after intramuscular injection is good; peak plasma concentrations of about 46 μg/ml have been achieved within 1 hour of a 1-g dose. Aztreonam is about 56% bound to plasma proteins. It is widely distributed in body tissues and fluids, including bile. Diffusion into the CSF is poor unless the meninges are inflamed. It crosses the placenta and enters the foetal circulation; small amounts are distributed into breast milk. Aztreonam is not extensively metabolised. The principal metabolite is inactive and is formed by opening of the beta-lactam ring; it has a much longer half-life than the parent compound. Aztreonam is excreted mainly in the urine, by renal tubular secretion and glomerular filtration; about 60 to 70% of a dose appears within 8 hours as unchanged drug with only small quantities of metabolites. Only small amounts of unchanged drug and metabolites are excreted in the faeces.

Aztreonam has a plasma half-life of about 1.7 hours. The half-life may be prolonged in neonates, in the elderly, in patients with renal impairment, and to some extent in those with hepatic impairment. Aztreonam is removed by haemodialysis and to a lesser extent by peritoneal dialysis.

Pharmacokinetics following inhalation

Based upon the urinary excretion data from healthy subjects (study CP-AI-001), after inhalation, mean Ae values are obtained from 6.5 – 10.4 % (bioavailability <11%).

Due to limitation of absorption, bioavailability decreases at high doses. Bioavailability data in patients are lacking, but it is considered that low systemic exposure is also the case for patients.
Plasma data are subject to a high variability. At high doses (285 mg), absorption is limited and systemic exposure increase less than dose proportional. There is no indication of accumulation of twice or thrice daily dosing AZLI. Data from the clinical studies in the target population indicate that disease severity (based upon FEV) seems to result in lower aztreonam plasma concentrations in case the predicted FEV was below 50%, compared to predicted FEV >50%.

The sputum data indicate that aztreonam sputum concentrations obtained in adults were in general higher than those obtained in adolescents. Sputum aztreonam concentrations in CF patients at early time points (10 min after single 75 mg dose inhalation) were 10-20 folds above MIC 90 values of *Pseudomonas aeruginosa* (32 μg/ml) but decreased significantly below the MIC 90 value at 4 hrs and trough values measured in the multiple dose clinical studies. For the clinical relevance of this regarding efficacy see assessment of clinical results. Furthermore, no relationship was observed between sputum and plasma aztreonam concentrations.

Of importance for inhaled products are the used nebulisers, as differences in nebulisers may affect delivery of aztreonam into the lungs. A clear overview is lacking on which device is used in the specific PK studies, although used eFlow nebulisers were reported to be comparable to the nebuliser meant for marketing. The applicant is requested to give an overview of the devices used in the specific studies and should discuss the eventual differences in devices and the impact of it on delivery of aztreonam**.**

- Special populations

No formal pharmacokinetic studies were done with AZLI in patients with renal impairment. Clinical studies with AZLI excluded patients with abnormal baseline renal function (defined as creatinine greater than two times the upper limit of normal range). The primary route of excretion for aztreonam is via the kidney and the label for aztreonam for injection recommends modifying the dose for renally

impaired patients after an initial dose of 500 mg, 1 g, or 2 g is given. However, given the low systemic exposures seen following AZLI administration, variations in renal function should not require dosage adjustments in patients treated with AZLI.

The proposed SPC of AZLI for inhalation indicates that aztreonam should be used with caution in such cases. Taking into account the indication, and the low systemic exposure after inhalation, this is considered acceptable, from a pharmacokinetic point of view.

No specific dose recommendations are stated in the SPC for patients with impaired hepatic function, and elderly as pharmacokinetics are not expected to be influenced to a clinically relevant extent.

No clear differences in plasma and sputum aztreonam concentrations are observed between children, adolescents and adults; however, this should be interpreted with caution due to the high inter-subject variability. The proposed SPC of AZLI 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.

- Pharmacokinetic interaction studies

Aztreonam is metabolised by hydrolysis, however, only to a small extent. Furthermore, animal data indicate that aztreonam may inhibit CYP3A4 activity. Considering the fact that aztreonam systemic exposure after inhalation is low, interactions at a systemic level are not expected. On the other hand, *in vivo* data indicated that aztreonam is mainly excreted via urine and 2-10% of the urinary metabolites remained unidentified. The metabolism/elimination was not studied in sufficient detail to draw conclusion on the metabolism of aztreonam and possible drug-drug interaction.

Pharmacodynamics

- Mechanism of action

Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis, followed by filamentation and cell lysis.

Prevalent important micro-organisms isolated from sputum of CF patients include *P. aeruginosa*, *S. aureus*, *Burkholderia cepacia,* and *Stenotrophomonas maltophilia,* Furthermore, *H. influenzae and S. pneumoniae, Mycobacteria*, and fungal species such as *Candida albicans* and *Aspergillus fumigatus* are encountered[5]. The antibiotic spectrum of aztreonam is limited to aerobic gram-negative bacteria. It includes *P. aeruginosa*, the most notorious pathogen in CF patients with lung infections.
It has no clinically meaningful activity against other important lung pathogens in CF patents.
Data present in the non-clinical part of the dossier regarding resistance show a decreased susceptibility, especially in Europe. Limited data on multidrug resistant isolates show that susceptibility in these isolates was low (10-20%). In the development of resistance, likely more mechanisms are involved.

Based on parenteral use, as for all β-lactam antibiotics, for aztreonam, time above MIC is the PK/PD parameter correlating best with efficacy. However, for the current indication, local concentrations in the lung are important. No discussion is provided regarding adequacy of local concentrations of AZLI in relation to high MICs (MIC90 of 1024 µg/ml reported in a recent European study).

In vitro, aztreonam showed evidence of at least some synergy with a wide range of antibiotics including tobramycin. No noteworthy antagonism was observed.

Local concentrations of aztreonam lysine were mostly well above MIC_{90} values of *P. aeruginosa*; however it is unclear whether sputum culture reflected the endotracheal flora or the tracheobronchial flora. In response to CHMP's request for a radioactive scintigraphic study the applicant stated that the

[5] G Valenza G et al. J Cyst Fibros. 2008 Mar;7(2):123-7. Prevalence and antimicrobial susceptibility of micro-organisms isolated from sputa of patients with cystic fibrosis.

scintigraphy technique cannot provide local concentrations beyond those already known from analysis of aztreonam sputum concentrations. The technique cannot provide local concentrations or even relative concentrations as requested. The only currently available method to determine local aztreonam concentrations in the small airways is analysis of sputum concentrations following AZLI administration. Applicant proposed a revised text for section 5.1 of the SmPC taking into account the CHMP's comments.

Overall, the dossier contained insufficient coverage of the microbiological epidemiology of relevant pathogens multi drug resistant strains in CF patients especially those with chronic *Pseudomonas aeruginosa* infection. Additional data were provided, indicating that high levels of baseline multi-drug resistant *PA* and *beta*-lactam antibiotic resistance were observed among CF patients in Study CP-AI-006; whereas lower beta-lactam antibiotic resistance were observed among CF patients in the placebo-controlled studies. The presence of multi-drug resistant *PA* and beta-lactam antibiotic resistance at baseline seems to affect the clinical outcome (improvement magnitude) notably.

In the open follow-up Study CP-AI-006, a trend toward increasing MIC values for beta-lactam antibiotics was observed during AZLI therapy, which was more pronounced for patients in the AZLI BID group. In contrast, a trend toward decreasing MIC values for aminoglycoside antibiotics was observed during AZLI therapy, particularly for patients in the AZLI TID group. The latter data should be interpreted with caution due to the design of the study.

Further data on resistance are required from ongoing Phase III comparative study with AZLI versus Tobi. These comparative results are also of critical importance for the definitive assessment of the efficacy and safety of AZLI in the target population.

- Primary and Secondary pharmacology

The active substance aztreonam is well known based on the long-standing experience with the systemic (IV and IM) use at higher dose levels than presently proposed for AZLI for the treatment of infections associated with aerobic gram-negative bacteria. Therefore the applicant has not conducted formal primary pharmacodynamic studies with AZLI.

No secondary pharmacodynamics studies were performed. The effects of inhaled AZLI on central nervous system function have not been assessed by specific safety pharmacology studies.

Clinical efficacy

Efficacy data are derived from four clinical studies: A Phase II (CP-AI-003) safety and efficacy study in adolescent and adult CF patients and two Phase III studies [CP-AI-007 (AIR-CF1) and CP-AI-005 (AIR-CF2)] which evaluated AZLI administered for 28 days (1 course). In addition an ongoing open-label uncontrolled follow-on study [CP-AI-006 (AIR-CF3)] is provided which evaluates the long-term safety and effects on disease related endpoints with multiple courses of AZLI treatment, with 28 days between courses.

Table. 3. Main studies

Study	Design	AZLI Dose	Location	ITT population (treated)
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
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
CP-AI-006 (ongoing)	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		207 (82 BID, 125 TID) at the 01-03- 2007 cutoff

The main inclusion criteria for the latter study were patients aged ≥ 6 years with CF, who had completed either study CP-AI-005 or CP-AI-007 or who withdrew from either of these studies due to need for anti-pseudomonal antibiotics or due to an adverse event (AE) unrelated to study medication tolerability.

In the two pivotal Phase III studies a newly developed patient reported outcome (PRO) measure was used, the CFQ-R which is a CF-specific quality of life measure encompassing both generic and CF specific domains. Three symptom scales (respiratory symptoms, digestive symptoms and weight) are included along with an overall general health perceptions domain.

The applicant designed two studies (protocols CP-MCID-001 and the TNS phase of CP-AI-005) to determine the minimal clinically important difference (MCID) measured by the CFQ-R respiratory symptoms domain. In both studies, MCID estimates were based on data obtained before and after 28 days of treatment with TNS. Part of these evaluations was to use the global rating of change questionnaire (GRCQ[6]) to support change in CFQ-R Respiratory domain scores. The magnitude of improvement in respiratory symptoms, as measured by responses to the GRCQ-Respiratory, was used to categorize patients as to whether they had experienced minimal, moderate, large, or no changes in respiratory symptoms during TNS treatment.
The results reported for CP-AI-007 represent the first use of a PRO instrument as the primary endpoint in a CF registration trial.

The usefulness of CFQ-R as a primary endpoint in confirmatory clinical trials is not sufficiently validated though (see further). Therefore, in the present assessment extra emphasis will be put on the lung function endpoints such as changes in both FEV1 (L) and FEV1 % predicted[7] which were included as secondary endpoints in the controlled and open label Phase III AZLI trials in the present application.

[6] CFQ-R: is a CF-specific, patient-reported outcome measure that includes both generic and CF-specific HRQOL domains.
[7] The availability and acceptance of spirometry equipment, standardized methods of performance and reference standards for values have led to FEV_1 becoming the most widely accepted and useful parameter for testing lung function both in routine clinical management of CF patients and in clinical trials of new therapies. FEV_1 is the strongest clinical predictor of survival among CF patients. Measuring sustained benefit to the patient as measured by lung-function especially FEV_1 after multiple courses of inhalational antibiotic therapy is considered as an important pivotal evaluation in the assessment of such products. Because lung volume is related to age, gender and height, absolute measures of FEV_1, measured in liters (l), do not provide a useful means to compare pulmonary function among patients who may differ in size and other relevant anthropomorphic variables. Therefore, FEV_1 (l) is often converted to values adjusted for age, gender and height using an equation developed by Knudson and has been the most commonly used outcome measure for CF clinical trials.

Microbiology endpoints included change in *PA* sputum density, treatment-emergent isolation of other bacterial respiratory pathogens (*Staphylococcus aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, *Burkholderia cepacia* complex), and change in susceptibility of *PA* to aztreonam or other antibiotics. In order to assess the PA CFU density in sputum findings definitively, the applicant was requested to provide the overview tables together with patient listings for collected sputum volumes and CFU counts on which the Log10 PA CFUs were based. However, sputum volumes were not collected in the AZLI clinical studies, but a minimum of 0.5 ml sputum was required for quantitative analysis of *PA* CFU density. If the patient could not expectorate, an oropharyngeal swab was collected for organism identification, but quantitative analysis could not be performed. Semi-quantitative analysis of *PA* CFU density was conducted for sputum sample volumes below 0.17 ml.

- Dose response study

Study CP-AI-003. This Phase II study was a multi-centre, double-blind, placebo-controlled trial (in 21 centres in the USA, but 20 centres recruited) and attempted to study safety and efficacy effects of self- administered AZLI 75 mg BID and 225 mg BID by inhalation.

Up to 138 CF patients were to be randomized into three cohorts (75 mg AZLI, 225 mg AZLI, and placebo). Patients were screened for inclusion in the trial within 7 days of the start of the treatment period. After randomization, each patient was instructed on the use of the eFlow® Electronic Nebuliser (eFlow). Patients were instructed to self-administer one dose twice-daily for 14 days, with the two daily doses being separated by at least 8 hours. Patients self-administered the first dose and one of the Day 7 doses at the clinic (Visits 2 and 3), and the remaining doses were self-administered at home. Patients returned to the clinic at the end of the treatment period (Day 14, Visit 4) and for a follow-up visit 14 days after the end of the treatment period (Day 28, Visit 5).

Table 4. Number of Patients Planned, Enrolled, and Analyzed in Study CP-AI-003

	Treatment			Total
	Placebo	75 mg AZLI	225 mg AZLI	
Planned	46	46	46	138
Safety Dataset [a]	31	37	37	105
ITT Dataset [a]	32	38	35	105
PP Dataset [a]	29	34	31	94

Some patients did not receive their treatments as randomized.
a. Data are presented for patients by treatment as received in the Safety and PP data sets and for patients by treatment as randomized in the ITT dataset.

The patients were >13 years of age (mean ±SD: 26.0± 10.2; only approx. ¼ between 13-18 years old) with *PA* and $FEV_1 \geq 40\%$ of predicted value who had not used anti-*PA* or macrolide antibiotics within 56 days were enrolled.

The primary efficacy variable was the percent change from pretreatment Day 0 to Day 14 in FEV1.

The following microbiology variables were assessed:

• Disappearance or appearance of other pathogens (*Staphylococcus aureus, Burkholderia cepacia* [appearance only], *Stenotrophomonas maltophilia, Achromobacter xylosoxidans*) from Day 0 to Day 7 and to Day 14

• Change in MIC50 and MIC90 of aztreonam for PA from Day 0 to Day 28

Post hoc exploratory analyses were performed by the sponsor to assess data by disease severity, with the disease severity categories separated at 75% rather than at 60% FEV1, and by BD use (BD users and non-users). By-subgroup analyses were performed on baseline and demographic data, change in

log10 CFU data, and spirometry change data. Spirometry change data were also analyzed by placebo subgroup (placebo-75 and placebo-225). Extent of exposure data were re-analyzed by BD use.

Efficacy results

There was an increase in adjusted mean percent change in FEV1 (L) from Day 0 to Day 14 in all treatment groups (4.08% in the placebo group, 6.20% in the 75 mg AZLI group, and 7.71% in the 225 mg AZLI group).

There was no significant difference in the mean percent change in FEV1 from Day 0 to Day 14 between the 225 mg AZLI and placebo treatment groups, either overall (treatment difference: 3.62%; CI: –1.50, 8.75) or for any of the subsets tested (disease severity [< 60 or ≥ 60% FEV1 percent predicted], age, gender, and MIC category [≤ 8 or > 8 μg/mL]) for the ITT or PP datasets.

There was an increase in adjusted mean percent change in FEV1 from Day 0 to Day 7 in all treatment groups (5.03% in the placebo group, 7.59% in the 75 mg AZLI group, and 9.74% in the 225 mg AZLI group). The difference of 4.71% between the 225 mg AZLI and placebo groups was statistically significant (CI: 0.06, 9.35), however, it was not confirmed by the PP dataset. None of the results for the remaining spirometry tests (FEV1, FVC, and FEF25–75) was statistically significant at any timepoint.

For FEV1 and FVC, mean absolute and percent changes were greater at Day 7 than they were at Day 14 for all treatment groups. For FEF25–75, the mean percent change from Day 0 at Day 7 was similar to that at Day 14 for the 75 mg AZLI group, and slightly smaller for the 225 mg AZLI group.

There was a mean reduction in log10 *PA* CFUs at Days 7 and 14 in both AZLI treatment groups, and the mean reductions in the 225 mg group were slightly larger than those in the 75 mg AZLI group. The difference (CI) between the 225 mg AZLI and placebo groups in change in log10 *PA* CFUs from Days 0 to 14 of –2.146 (–3.029, –1.263) was highly statistically significant (p-value < 0.0001).

There were no trends in the numbers of patients who required hospitalization/emergency treatment or anti-*PA* antibiotics during the trial.

There was no statistically significant difference between the placebo and 225 mg AZLI groups in the numbers of patients unable to expectorate sputum at Day 14. There was a potential loss of power in the trial because there were only 105 evaluable patients in the ITT dataset, which was less than the planned sample size of 138, and this may have contributed to the lack of statistical significance shown in the results.

Microbiology results

The majority of patients in each treatment group showed no changes in the presence or absence of the pathogens tested. After dosing, *PA* infection disappeared from two patients in the 75 mg AZLI group (Day 28), and three and seven patients in the 225 mg AZLI group (Days 7 and 14, respectively). *PA* infection did not disappear at any postdosing day for any patients in the placebo group. There were no notable differences between treatments in the numbers of patients becoming positive after dosing for any of the pathogens tested (*S aureus*, *B cepacia*, *S maltophilia*, or *A xylosoxidans*). There were no notable differences between treatment groups in the numbers of patients who were positive at Day 0 and became negative for any of the other pathogens tested.

There were no notable increases from Day 0 in MIC50 or MIC90 (using all *PA* isolates and the *PA* isolate with the highest MIC from each patient) in any treatment group, indicating there was no evidence of reduced susceptibility of *PA* to aztreonam.

There were no notable increases from Day 0 in the numbers of patients whose *PA* isolate with the highest MIC was above the parenteral susceptibility breakpoint for aztreonam (> 8 μg/ml) in either AZLI treatment group.

Results of Post Hoc Exploratory Analyses

The results of post hoc exploratory analyses suggested that FEV1 % predicted values were improved in patients with FEV1 values less than 75% of predicted at Day 0 in the 225 mg AZLI group after 7 days of treatment (with a treatment difference of 9.0% [CI:1.9,16.2]) but this effect was not maintained at Day 14. Bronchodilator use was associated with positive impact on the lung function.

The most common drug-related AE was cough, which was related to dose level in its incidence and severity.

Overall**,** the power of the trial to detect relevant differences between active treatments and placebo was compromised because of the small number of evaluable patients and the mild to moderate CF disease severity regarding lung function at baseline (approx. 80% had FEV1 ≥ 60% of predicted). Based on the above results, the applicant concluded to choose for a 28 day course AZLI 75 mg BID or TID dosing for further clinical Phase III trials.

- Main studies

CP-AI-005: A Phase 3, Double-blind, Multicentre, Randomised, Placebo-controlled Trial with Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary *P. aeruginosa* Requiring Frequent Antibiotics (AIR-CF2).

This trial was designed to assess the safety and efficacy of a 28-day treatment with Aztreonam Lysine for Inhalation (AZLI) and the ability of AZLI to maintain or improve clinical status following a 28-day course of Tobramycin Inhalation Solution (TNS, TOBI) therapy in cystic fibrosis (CF) patients with pulmonary *Pseudomonas aeruginosa* (*PA*).

CP-AI-007: A Phase 3, Double-blind, Multicentre, Multinational, Randomised, Placebo-controlled Trial Evaluating Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary *P. aeruginosa* (AIR-CF1)

This trial was designed to assess the safety and efficacy of a 28-day treatment with aztreonam lysine for inhalation (AZLI) (75 mg three times daily [TID]) compared to placebo in cystic fibrosis (CF) patients with lung disease due to *Pseudomonas aeruginosa* (*PA*) infection.

METHODS

Study design and participants

CP-AI-005 and CP-AI-007 were multi-centre, randomized, double-blind placebo-controlled trials in which 211 CF patients (all from the US; 56 centres) and 164 CF patients (53 sites in total, 40 in the US, 5 in Canada, 7 in Australia, and 1 in New Zealand) were included respectively. Mean ages (SD) were 26(10) and 27 (13) years respectively.

The design and treatment setting of these studies were not as such that they would qualify for the "on demand" maintenance therapy of chronic PA lung infection. Data indicated that included patients had to have stable pulmonary disease (and stable co-medication) and a recent positive sputum culture for *PA*, were >6 years of age with *PA* and $FEV_1 \geq 25\%$ to ≤ 75% predicted at Visit 1 and were treated with AZLI or placebo using the PARI eFlow Nebuliser for 28 days. Overall, ≥ 60 % of the patients in both studies had lung function FEV1 ≥ 50% of predicted at baseline.

In both studies, main exclusion criteria were patients who had a history of sputum or throat swab culture yielding *B. cepacia* in the previous 2 years. Similarly patients with a history of daily continuous oxygen supplementation or requirement for more than 2 L/minute at night were excluded. Similarly, patients with a chest radiograph at Visit 1 (or within the previous 90 days of Visit I), with abnormalities indicating a significant acute finding (eg, lobar infiltrate and atelectasis, pneumothorax, or pleural effusion) were excluded.

Pregnant females or females of child bearing potential who were lactating or (in the opinion of the investigator) not practising an acceptable method of birth control were also excluded.

Treatments

CP-AI-005: Patients were screened for eligibility at Visit 1 (Day -42) and returned to the centre for Visit 2 after a 14-day evaluation period. At Visit 2 (Day -28), patients were randomised and began a 28-day course of TNS. At Visit 3 (Day 0), following completion of the 28-day course of TNS, patients began treatment at the clinic with their randomised therapy, either AZLI (twice daily [BID] or three times daily [TID]) or volume-matched placebo (BID or TID), and continued treatment at home for a total of 28 days, with a clinic visit (including one of the daily doses) after 14 days of treatment (Visit 4 [Day 14]) and at the end of treatment (Visit 5 [Day 28]).

Patients returned for visits every 2 weeks for 8 weeks after the end of the AZLI/placebo treatment (Visits 6 to 9 [Days 42 to 84]). TNS was self-administered using the PARI LC PLUS® Jet nebuliser, and AZLI was self-administered using the PARI eFlow® Electronic Nebuliser (eFlow). All doses of AZLI/placebo were administered after using a short-acting bronchodilator.

In this study, all patients had received at least 3 courses (mean 5.3) of TNS (TOBI) in the previous 12 months; in addition, inhaled Colistin (antibiotic) was also used in some patients in pre-study period. The trial population was generally extensively co-medicated with medicinal products for obstructive airway diseases (99% of patients) such as salbutamol (89% of patients), fluticasone propionate w/ salmeterol (56% of patients), and dornase alpha (85% of patients). Systemic azithromycin was used in 70% of the patients.

CP-AI-007: Patient eligibility was initially assessed at a Screening Visit that occurred 7 to 14 days prior to the baseline visit (Day 0). Those patients who continued to meet eligibility criteria at Day 0 were randomized and began a 28-day course of AZLI TID or placebo TID. Patients returned for clinic visits at Day 14, an end of treatment visit at Day 28, and a follow-up visit 14 days after the last dose of the trial drug (Day 42). AZLI/placebo was self-administered using the PARI eFlow® Electronic Nebuliser (eFlow). All doses of AZLI/placebo were administered after using a short- or long-acting bronchodilator. Patients in this trial could be eligible to enrol in an open-label follow-on trial, CP-AI-006.

In this trial, the patients were co-medicated with medicines for obstructive airway diseases (93% of patients) such as salbutamol (79% of patients), fluticasone propionate w/ salmeterol (40% of patients). Azithromycin use was not allowed.

In both studies a bronchodilator (BD) was administered before each dose of AZLI or placebo to potentially improve drug deposition and to prevent bronchospasm.

There was generally a high level of treatment compliance in the trials ($\geq$90%, by counting used and unused vials).

Outcomes/endpoints

CP-AI-005:

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 the four symptoms was present, he/she was considered an event patient for the primary analysis.

The *secondary* efficacy endpoints were as follows:

a. Clinical symptoms as assessed by the Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain
b. Change in pulmonary function (forced expiratory volume in 1 second [FEV_1], FEV_1 percent of predicted, forced vital capacity [FVC] and forced expiratory flow from 25% to 75% [FEF_{25-75}])
c. Hospitalization: time to hospitalization, number of days hospitalized, proportion of patients hospitalized, and percent of days hospitalized
d. School and/or work missed: number of missed school/work days, proportion of patients missing school/work, and percent of school/work days missed
e. Change in CFQ-R non respiratory domains
f. Physician's and patient's assessment of change in symptoms using the Global Rating of Change Questionnaire (GRCQ)
g. Percent change in weight
h. Change in body mass index (BMI)
i. Change in CF symptoms and severity
j. Change in patient's ability to produce sputum
k. Change in $\log_{10}$ PA colony-forming units (CFUs) in sputum

CP-AI-007:

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.

The key secondary efficacy endpoints were as follows:
a. Percent change in FEV_1 from Day 0 to Day 28
b. Change in $\log_{10}$ PA colony-forming units (CFUs) in sputum from Day 0 to Day 28
c. Proportion of patients receiving IV or inhaled anti-PA antibiotics other than trial drug through nominal Day 42
d. Proportion of patients hospitalized through nominal Day 42
e. Other secondary efficacy endpoints were as follows:
f. Change from baseline (Day 0) to Day 14 and Day 42 in clinical symptoms as assessed by the CFQ-R respiratory domain
g. Change in pulmonary function (FEV_1 percent of predicted, AUC analysis of change in FEV_1 [L] from Days 0 to 42, change in forced vital capacity [FVC], and change in forced expiratory flow from 25% to 75% [FEF_{25-75}])
h. Change in the CFQ-R non respiratory domains
i. Percent of days and number of days hospitalized
j. Use of non trial drug anti-PA antibiotics (oral and overall)
k. Change in CF symptoms and severity
l. Missed school and/or work days due to CF
m. Change in patient's ability to produce sputum
n. Percent change in weight
o. Change in Body Mass Index (BMI)

Measurements of the secondary endpoints were similar to those in study CP-AI-005.
This holds also for obtaining and handling of sputum for microbiological evaluations.

In both studies other evaluations were aztreonam concentrations in plasma and sputum and microbiological measurements such as disappearance or appearance of other pathogens (*S. aureus*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*); and MICs of aztreonam for *PA*.

Furthermore, criteria for evaluation of *Safety* were AEs, hematology and serum chemistry, vital signs, and airway reactivity.

Randomisation and sample size

CP-AI-005: Patients were randomized centrally in a 2:2:1:1 fashion to one of four treatment groups: AZLI BID, AZLI TID, placebo BID, or placebo TID. The randomization code was generated by an independent third party.

CP-AI-007: The planned trial size was approximately 140 patients randomised in a 1:1 ratio to AZLI TID or placebo TID. There were 164 patients included in both the Safety population and the Intent-to-treat (ITT) population.

Randomization was stratified by disease severity (FEV_1 percent of predicted ≥ 25% to ≤ 50% and > 50% to ≤ 75%).

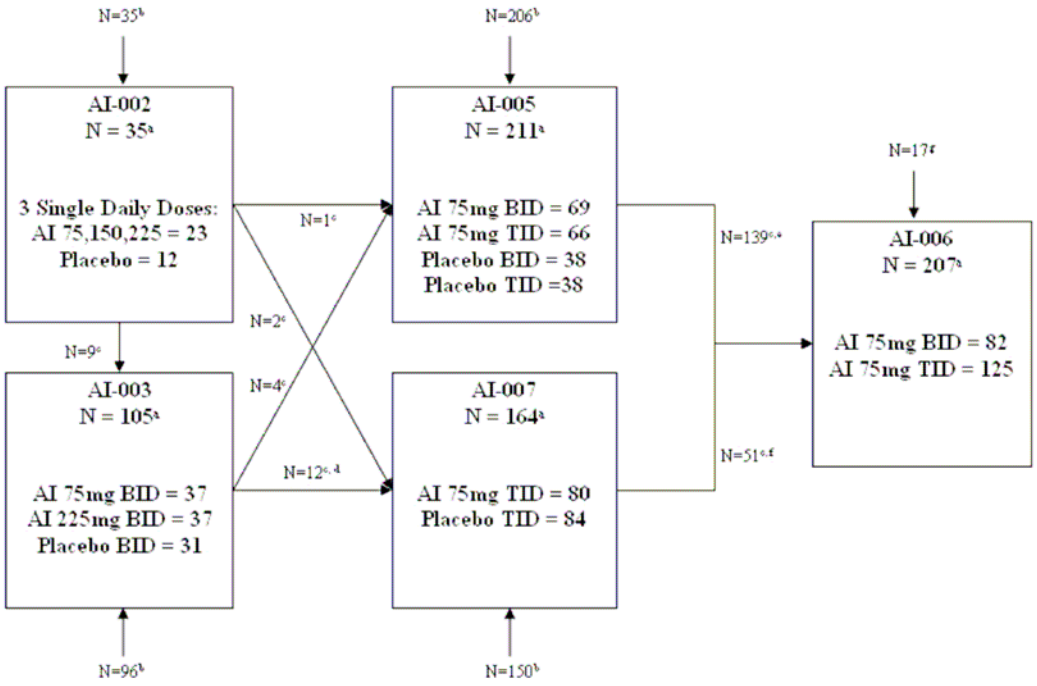
Blinding (masking)

For both studies, treatment assignments of AI or placebo were blinded to trial patients, the sponsor, the contract research organizations, and other trial vendor(s) and trial personnel, except for the delegated personnel who reviewed the randomization lists and drug allocation for accuracy.
The investigator was to contact the medical monitor if he/she considered unblinding to be necessary for the safety of the patient. The DMC could decide at any point that unblinding was necessary and could temporarily stop the trial for concerns of patient safety.

RESULTS

Participant flow/ Numbers analysed

Many patients took part in more than one efficacy studies. The figure below illustrates the participation of patients across studies.



[a] Numbers of patients shown are "as treated" in each study (with AI or placebo).
[b] Number of patients who enrolled in the study following the arrow as their initial study.
[c] Number of patients who enrolled in both studies connected by arrow, in the order shown by the arrow.
[d] 2 of these patients also participated in AI-002 prior to AI-003.
[e] 3 of these patients also participated in AI-003 prior to AI-005, 1 of these patients also participated in AI-002 prior to AI-005.
[f] 7 of these patients also participated in AI-003 prior to AI-007.
[g] Prior to AI-006 these patients participated in AI-005 but were not treated.

Number of Subjects for study **CP-AI-005**:

	Treatment				
	Placebo		75 mg AZLI		
Population	**BID**	**TID**	**BID**	**TID**	**Total**
Planned	—	—	—	—	Approx 250
Enrolled	41	41	82	82	247[a]
Safety	38	38	69	66	211
ITT	38	38	69	66	211
PP	37	35	62	59	193

Patients were randomised in a 1:1:2:2 ratio to Placebo BID:Placebo TID:AZLI BID:AZLI TID.
The Safety and ITT populations were identical.
[a] One patient received TNS but was not randomised and is included in the Enrolled total only.

CP-AI-007: There were 164 patients included in both the Safety population and the Intent-to-treat (ITT) population. Patient flow is shown hereafter:

Table 5: Populations for Analysis (Safety, ITT, and PP) and Reasons for Exclusion from Populations by Actual Treatment Received.

	Placebo (N = 84) n (%)	**75 mg Aztreonam lysine (N = 80) n (%)**	**Total (N = 164) n (%)**
No. of patients randomized	83	83	166
No. of patients in Safety population	84 (100)	80 (100)	164 (100)
Reasons for exclusion from Safety population: Patient did not receive at least one dose of AI/placebo	0	0	0
No. of patients in ITT population[a]	84 (100)	80 (100)	164 (100)
Reasons for exclusion from ITT population: Patient did not receive at least one dose of AI/placebo	0	0	0
No. of patients in PP population by actual treatment	71 (84.5)	74 (92.5)	145 (88.4)
Reason for exclusion from PP population:	-	-	-
Did not comply with an inclusion or exclusion criterion, which based on medical review, impacted endpoints	1 (1.2)	0	1 (0.6)
Did not use at least 66% of vials based on relative compliance or was not treated for at least 14 days	7 (8.3)	3 (3.8)	10 (6.1)
Last dose before Visit 4 (Day 28) was >7 days before Visit 4 date	5 (6.0)	3 (3.8)	8 (4.9)
Used antipseudomonal antibiotic between Visit 1 and 7 days before Visit 4 (Day 28)	5 (6.0)	1 (1.3)	6 (3.7)
Recorded changes in antipseudomonal, high dose ibuprofen, (prophylactic use), systemic corticosteroid therapy use, dornase alfa, or chest physiotherapy between Visit 1 (Day -14) and Visit 4 (Day 28	4 (4.8)	1 (1.3)	5 (3.0)
Patient was given non sequential randomization number for the stratum	1 (1.2)	0	1 (0.6)
Attended pre-Visit 4 early termination visit more than 7 days after starting an anti pseudomonal antibiotic	5 (6.0)	1 (1.3)	6 (3.7)

A patient may be excluded for more than one reason.
Two patients randomized to receive AI were withdrawn before receiving trial drug.
a One Patient was randomized to receive 75 mg AI TID but was treated with placebo in error

Recruitment

In **CP-AI-005** date of first enrolment was 24 February 2005 and date of last follow-up was September 2006.

In **CP-AI-007** date of first enrolment was 10 June 2005 and date of last follow-up was April 2007.

Conduct of the study

CP-AI-005

- The Cystic Fibrosis Foundation (CFF) formed a Data Safety Monitoring Board (DSMB) to monitor all phases of CF drug development and to develop a core of expertise specifically related to CF.

An independent Data Monitoring Committee (DMC), a trial-specific subcommittee of the CFF-DSMB, was formed to monitor safety for this trial. The DMC was chosen by the DSMB Chair based on trial content and patient safety concerns. The appointed DMC Chair and the sponsor had a DMC charter with guidelines for notification and data safety reviews, including comparison of safety data from the BID and TID treatment groups.

- Two *unblinded interim safety reviews* were submitted to the CFF-DSMB. The first review was performed on data up to 25 August 2005, when 39 patients had been randomized. The second review was performed on data up to 06 December 2005, when 128 patients had been randomized. These reviews included safety data and were prepared by an unblinded independent party that had no other role in the trial and was not involved in analysis of the trial at the time of database lock.

- The *protocol amendment* was issued 17 February 2005. This amendment was introduced to amend among others the list of secondary efficacy endpoints. However, the protocol amendment was issued before any patients were screened for participation in the trial, therefore the trial was conducted according to the amended protocol for all patients.

- The majority of patients in this trial were randomized after Day -28, but before Day 0, for practical reasons. This may have affected the order in which patients were randomized to the trial, however because complete treatment blocks were maintained, there should be no noticeable effect on the results of the trial.

CP-AI-007

The Cystic Fibrosis Foundation (CFF) involvement was largely as in the former study.
No formal DMC interim analyses were planned or conducted for CP-AI-007 although it was planned.
Several protocol amendments were performed.

Baseline data

Treatment groups were well balanced for most demographic and baseline characteristics (see further for Table 10: Demographic and Baseline Characteristics: Integrated Phase 3 Controlled Trials).

Outcomes and estimation

CP-AI-005

The primary efficacy variable was the time to need for inhaled or IV antipseudomonal antibiotics due to pre-defined symptoms (decreased exercise tolerance, increased cough, increased sputum/chest congestion, decreased appetite). By chance, more patients who subsequently responded to TNS therapy were randomized to the TID arm.

A significant difference from the pooled placebo group in time to antibiotic need was observed in the AZLI BID group (p = 0.0019), but not in the AZLI TID group (p=0.1816), based on all events, including those occurring beyond 56 days after the end of AZLI/placebo therapy (Day 84, end of controlled trial). The median time to need for inhaled or IV antibiotics due to pre-defined symptoms (measured from Day 0) was estimated to be 21 days longer in the pooled AZLI group than in the pooled placebo group (92 days vs. 71 days, p = 0.0070). See table 6 for the results of the primary endpoint.

Table 6. Study CP-AI-005 Main efficacy results: Primary endpoint (shaded)

Efficacy Endpoint	***Pooled Placebo (n = 76)***	***AZLI BID (N =69)***	***AZLI TID (N =66)***	***Pooled AZLI (n = 135)***	***TD (P-value)***
Primary Endpoint					
Use of non-study anti-*PA* antibiotics					
Median time (Days) to need of IV or inhaled antibiotics	71	ne	87	92	21 (0.0070[a])
% of patients using IV or inhaled antibiotics	56.6	36.2	43.9	40.0	—
% of patients using antibiotics overall	60.5	47.8	59.1	53.3	—

a p-values are based on the Log-Rank test and compare AZLI Pooled vs Placebo Pooled.

Notes: - not applicable; TD = Treatment Difference; ne = not estimable

As to the main secondary endpoints, a significant difference from the pooled placebo group in change in pulmonary function (FEV_1, FEV_1 % predicted) was observed in both AZLI treatment groups at day 28. A similar pattern of results were obtained for *PA* CFU density in sputum. The effects of BID and TID AZLI were similar (table 6). In order to assess the *PA* CFU density in sputum findings definitively, applicant was requested to provide the overview tables together with patient listings for collected sputum volumes and CFU counts on which the Log10 *PA* CFUs were based (these were denoted as being available on request).

The response to AZLI treatment as measured by mean (adj.) change in percent change in FEV_1 (L) decreased importantly from Day 28 to Day 42 seemingly more in the AZLI TID group. The same holds for the mean (adjusted) change in FEV_1 % predicted. A similar pattern of results were obtained for PA CFU density in sputum. At two weeks post-treatment, CFU density increased, although respiratory symptoms and pulmonary function still showed some improvement over baseline for AZLI-treated patients, *PA* CFU density was near, or exceeded, baseline values.

Based on patient perception of change in their respiratory symptoms domain scores as measured with the newly developed variable CFQ-R (a change of 5 points being the minimum change that can be reliably detected by an individual patient on this scale), clinically significant improvement in respiratory symptoms among BID and TID AZLI-treated patients compared to placebo at both Days 14 and 28 were observed.

Domains of the CFQ-R related to for example physical functioning, role limitations/school performance, weight disturbances, and treatment burden were also reported to show some improvement in this short-term study.

Overall**,** the observed improvements in pulmonary function and PA CFU density obtained with AZLI 75 mg BID or TID in this short –term study of 1 course of 28 days versus placebo in extensively TOBI pre-treated CF patients with chronic PA lung infection are encouraging. Of note, however, these patients had completed a 28-day TNS course immediately prior to AZLI therapy and showed a 0.9% mean increase in FEV_1 % predicted during the TNS run in period. The observed effects within AZLI patients should be considered as the resultant of the TNS and AZLI courses. These improvements diminished importantly within 2 weeks after cessation of the AZLI treatment with PA CFU density nearing, or exceeding, baseline values. The AZLI TID seemed to perform slightly better with regard to the latter parameter. In order to assess the PA CFU density in sputum findings definitively, applicant was requested to provide the overview tables together with patient listings for collected sputum volumes and CFU counts on which the Log10 PA CFUs were based. [However, sputum volumes were not available; see earlier comment above)]. As expected the median time to need of inhaled or IV antibiotics due to pre-defined symptoms (measured from Day 0) was longer in the AZLI treated patients (pooled) than in the placebo treated patients (pooled).

As to CFQ-R, mean (adjusted) change in respiratory symptoms at Day 28 appeared to confirm the effects observed on the pulmonary function variables. Of note, however, the rather high categorical placebo response (37 % improved versus 51.5% in the pooled AZLI group with improvement defined as increase in score of ≥ 5 points); CFQ-R measurements at 2, 4 and 6 weeks post-treatment were not performed. In the controlled phase of the study the correlations between percent change in FEV1 and actual change in CFQ-R respiratory domain scores were poor in the AZLI BID, AZLI TID and pooled placebo groups (correlation coefficient = 0.33, 0.24, and 0.33 for AZLI BID, AZLI TID, and pooled placebo, respectively).

Table 7. Study CP-AI-005 Main secondary efficacy results

Efficacy Endpoint	*Pooled Placebo (n = 76)*	*AZLI BID (N =69)*	*AZLI TID (N =66)*	*Pooled AZLI (n = 135)*	*TD 95% CI* (p-value)*
Main Secondary Endpoints					
Change in pulmonary function					
Mean (adjusted) percent change in FEV_1 at Day 28	–2.4	3.8	4.0	3.9	6.3 2.50, 10.060[a] (0.0012)
Mean (adjusted) percent change in FEV_1 at Day 42	–5.0	1.6	0.1	0.9	5.8 1.97, 9.72[a] (0.0033)
Mean (adjusted) percent change in FEV_1 predicted at Day 28	-2.52	4.01	4.15	4.08	6.6 2.81, 10.40[a] (0.0007)
Mean (adjusted) percent change in FEV_1 predicted at Day 42	–5.14	1.83	0.26	1.06	6.2 2.26, 10.15[a] (0.0022)
Change in log_{10} ***PA* CFUs** in sputum					
Mean (adjusted) change in sputum log_{10} *PA* CFUs at Day 28	0.225	–0.49	–0.37	–0.434	–0.66 -1.13,-0.19[b] (0.0059)
Mean (adjusted) change in sputum log_{10} *PA* CFUs at Day 42	0.171	0.46	0.02	0.244	0.074 –0.43, 0.57[b] (0.7703)
Clinical symptoms as assessed by **CFQ-R** respiratory symptoms domain					
Mean (adjusted) change[c] in respiratory symptoms at Day 14	–2.06	2.86	4.10	3.47	5.53 1.35, 9.70 (0.0097)
Mean (adjusted) change [c] in respiratory symptoms at Day 28	–0.66	5.10	3.56	4.34	5.01 0.81, 9.21 (0.0196)
Categorical result[@]: % of patients who improved at Day 28	37.0	55.2	47.7	51.5	—
% of patients who worsened at Day 28	38.4	26.9	29.2	28.0	—

* 95% CI; Treatment difference: pooled AZLI – pooled placebo

@ Improved – increase in score of ≥ 5 points (MCID), worsened – decrease in score of ≥ 5 points

a From ANCOVA models including terms for treatment group as a fixed effect and Day 0 FEV_1 % predicted as a covariate.

b From ANOVA model including treatment and baseline highest aztreonam MIC for *PA*.

c From ANCOVA. Baseline (Day 0) CFQ-R respiratory domain score included as a covariate.

Notes: - not applicable; TD = Treatment Difference

CP-AI-007

The primary efficacy variable in this study was CFQ-R based on patient perception of change in their respiratory symptoms domain scores. Clinically important improvement in respiratory symptoms among TID AZLI-treated patients compared to placebo at both Days 14 and 28 were observed. Treatment difference in favour of AZLI was (9.71) at Day 28. The response to AZLI treatment as measured by mean (adjusted) change in CFQ-R respiratory domain score decreased from 7.08 at Day 28 to 0.62 at Day 42 (14 days after the end of treatment) but the treatment difference between AZLI treatment and placebo remained statistically significant. See table 8 for primary endpoint results.

Table 8 Study CP-AI-007 Primary efficacy results

Efficacy Endpoint	***Placebo (n = 84)***	***AZLI (n = 80)***	***TD***	**95% CI** (p-value)
Primary Endpoint				
Clinical symptoms as assessed by CFQ-R respiratory symptoms domain				
Mean (adjusted) change in respiratory symptoms at Day 14	–0.98	7.01	7.98	3.50, 12.47[a] (0.0006)
Mean (adjusted) change in respiratory symptoms at Day 28	–2.63	7.08	9.71	4.31, 15.11[a] (0.0005)
Mean (adjusted) change in respiratory symptoms at Day 42	–5.71	0.62	6.33	1.22, 11.43[a] (0.0154)
Categorical result[@]: % of patients who improved at Day 28	37.3	56.3	—	0.0055[b]
Categorical result[@]: % of patients who improved at Day 42	30.1	45.0	—	
% of patients who worsened at Day 28	44.6	25.0	—	
% of patients who worsened at Day 42	51.8	36.3	—	

@ Improved – increase in score of ≥ 5 points (MCID), worsened – decrease in score of ≥ 5 points

a From ANCOVA including baseline (Day 0) CFQ-R respiratory symptoms domain score and disease severity as covariates.

b p-values from Cochran-Mantel-Haenszel test stratified by categorized baseline response and baseline disease severity stratum.

(-) not applicable

At Day 28, AZLI treated patients in the more severe disease category (FEV1 ≤ 50% of predicted; n = 60: 30 AZLI and 30 placebo) showed an adjusted mean change in CFQ-R respiratory domain score of 4.22 (with treatment difference of 8.25 and 95% CI : -1.14, 17.64; p= 0.0839) versus 10.14 (with treatment difference of 10.90 and 95% CI : 4.16, 17.64 ; p = 0.0018) in patients with the less severe disease category (FEV_1> 50% of predicted; n = 103: 50 AZLI and 53 placebo).

Similarly, AZLI-treated patients responded significantly better than placebo treated patients at day 28 in the main secondary endpoints change in pulmonary function and *PA* CFU density in sputum. See the following table. The response to AZLI treatment as measured by mean (adj.) change in percent change in FEV_1 (L) decreased from 3.58 at Day 28 to 1.55 at Day 42 but the treatment difference between AZLI treatment and placebo remained statistically significant.

Table 9 Study CP-AI-007 Main secondary efficacy results

Efficacy Endpoint	*Placebo (n = 84)*	*AZLI (n = 80)*	*TD*	**95% CI** (p-value)
Main Secondary Endpoints				
Change in pulmonary function				
Mean (adjusted) percent change in FEV_1 at Day 28	–2.4	7.9	10.3	6.29, 14.30 (< 0.0001)
Mean (adjusted) percent change in FEV_1 at Day 42	–2.6	3.1	5.7	2.07, 9.4 (0.0024)
Mean (adjusted) percent change in FEV_1 predicted at Day 28	–1.68	3.58	5.25	3.21, 7.30 [a] (< 0.0001)
Mean (adjusted) percent change in FEV_1 predicted at Day 42	–1.56	1.55	3.11	1.10, 5.13 [a] (0.0027)
Change in log_{10} *PA* CFUs in sputum				
Mean (adjusted) change in sputum log_{10} *PA* CFUs at Day 28	0.069	–1.384	–1.453	-2.12, -0.79[b] (< 0.0001)
Mean (adjusted) change in sputum log_{10} *PA* CFUs at Day 42	–0.010	–0.078	–0.069	-0.67, 0.54[b] (0.8218)
Use of non-study antipseudomonal antibiotics				
Median time (Days) to need of IV or inhaled antibiotics	ne	ne	—	
% of patients using IV or inhaled antibiotics	22.6	15.0	—	0.2364[c]
% of patients using oral antibiotics	25.0	11.3	—	0.0267[c]
% of patients using antibiotics overall	35.7	17.5	—	0.0131[c]

a From ANCOVA models including terms for treatment group as a fixed effect and Day 0 FEV_1 % predicted as a covariate.

b From ANOVA model including treatment and baseline disease severity as fixed effects in the model.

c p-values are based on Fisher's Exact test.

Notes: - not applicable; TD = Treatment Difference

PA CFU density adjusted mean change improved significantly in favour of AZLI at Day 28. At Day 42, *PA* CFU density increased and became slightly lower than baseline values in both treatment groups.

Disease severity had a similar pattern of effect on mean (adj.) change in percent change in FEV_1 (L) as for CFQ-R respiratory domain scores. At Day 28, patients in the more severe disease category (FEV1 ≤ 50% of predicted; n = 60: 30 AZLI and 30 placebo) showed an adjusted mean percent change in FEV1 of 6.3% on AI compared with -4.0% on placebo. Patients in the less severe disease category (FEV_1> 50% of predicted; n = 104: 50 AZLI and 54 placebo) trended towards greater improvement at Day 28 (9.5%) on AZLI than those in the more severe disease category and less deterioration (-0.6%) on placebo than those in the more severe disease category. The treatment differences between AZLI and placebo were significant regardless of disease severity category, and results for the two disease severity categories were similar: 10.3%, p = 0.0061, in the more severe category, and 10.1%, p <0.0001, in the less severe disease category.

Fewer hospitalizations, due to pulmonary exacerbation were observed in the AZLI treated group compared to placebo between Days 0 and 42 (2/4 and 8/12 patients hospitalized resp.) and most of them were hospitalized after their last treatment dose.

Like in study CP-AI-005 domains of the CFQ-R related to for example physical functioning and weight disturbances were also reported to show some improvement in this short-term study.

Overall, the observed improvements in pulmonary function and PA CFU density obtained with AZLI 75 mg TID in this short –term study of 1 course of 28 days versus placebo less extensively TOBI pre-treated or dornase (and no oral azithromycin allowed) CF patients with chronic PA lung infection are encouraging. As in study CP-AI-005, these improvements diminished importantly within 2 weeks after cessation of the AZLI treatment with PA CFU density nearing baseline values with no significant difference between treatment groups. In order to assess the PA CFU density in sputum findings definitively Applicant is requested to provide the overview tables together with patient listings for collected sputum volumes and CFU counts on which the Log10 PA CFUs were based. However, sputum volumes were not available; see earlier comment above.

As expected, the median time to need of inhaled or IV antibiotics due to pre-defined symptoms (measured from Day 0) was longer in the AZLI treated patients than in the placebo treated patients but with no significant difference between treatment groups.
As to CFQ-R, mean (adjusted) change in respiratory symptoms at Day 28 appeared to confirm the effects observed on the pulmonary function variables. Of note, however, the rather sharp decline in the AZLI TID group almost to baseline value whereas the mean (adjusted) percent change in FEV_1 predicted at Day 42 was still substantial. The correlations between percent change in FEV1 and change in CFQ-R respiratory domain scores for the ITT (imputed data) population were poor in the AZLI TID and placebo group (correlation coefficient = 0.32 for both treatment groups).

Of note also the high categorical placebo response: 37 % and 56% of patients improved in the placebo and the AZLI group respectively, at Day 28. These rates decreased to 30% and 45% respectively, at Day 42.

- Analysis performed across trials (pooled analyses and meta-analysis)

Integrated analysis from studies CP-AI-005 and CP-AI-007

The data below presents integrated data from studies CP-AI-005 and CP-AI-007 showing that the treatment groups were well balanced for most demographic and baseline characteristics. There were more children (age ≤ 12 years) and fewer adults (age ≥ 18 years) in the pooled AZLI group than in the pooled placebo group. The proportion of children was higher in the TID group compared with the BID group. Overall, fewer than 10% of the enrolled patients were between the ages of 6 and 12, reflecting relatively small proportion (approximately 17%) of CF patients in the US with moderate to severe lung disease (FEV_1 < 70% predicted). The mean FEV_1 % predicted at baseline was approximately 55%.

Table 10. Demographic and Baseline Characteristics: Integrated Phase 3 Controlled Trials

	Placebo Pooled (N =160)	***AZLI***		
		75 mg BID (N =69)	***75 mg TID (N =146)***	***Pooled (N =215)***
Male n (%)	90 (56.3)	38 (55.1)	86 (58.9)	124 (57.7)
Mean (SD) Age (years)	29.9 (13.0)	26.5 (10.7)	25.9 (11.6)	26.1 (11.3)
Age Subgroup n (%)				
≥ 6 to ≤ 12 Years n (%)	5 (3.1)	4 (5.8)	16 (11.0)	20 (9.3)
> 12 to < 18 Years n (%)	23 (14.4)	13 (18.8)	22 (15.1)	35 (16.3)
≥ 18 Years n (%)	132 (82.5)	52 (75.4)	108 (74.0)	160 (74.4)
Race n (%)				
African American	0	3 (4.3)	0	3 (1.4)
Caucasian	151 (94.4)	61 (88.4)	139 (95.2)	200 (93.0)
Hispanic	8 (5.0)	5 (7.2)	7 (4.8)	12 (5.6)
Other	1 (0.6)	0	0	0
Mean (SD) Weight (kg)	61.2 (14.2)	57.2 (12.6)	58.9 (17.1)	58.4 (15.8)
Mean (SD) BMI (kg/m^2)	21.8 (3.5)	20.9 (3.3)	21.2 (4.3)	21.1 (4.0)

Mean (SD) FEV_1 (L)	1.87 (0.65)	1.90 (0.65)	1.89 (0.69)	1.89 (0.68)
Mean (SD) FEV_1 % Predicted	54.4 (15.3)	56.2 (15.6)	55.6 (14.9)	55.8 (15.1)
Disease Severity n (%)				
FEV_1 % Predicted ≤ 50%	60 (37.5)	24 (34.8)	52 (35.6)	76 (35.3)
FEV_1 % Predicted > 50%	100 (62.5)	44 (63.8)	94 (64.4)	138 (64.2)

The major difference in the patient groups was their prior use of TNS due to different entry criteria. In study CP-AI-005 the average number of TNS courses used in the previous 12 months was 5.3, compared with 1.8 for CP-AI-007. There were also important differences in co-medications (such as use of dornase and oral azithromycin).

Table 11 Number (%) of Patients Who Used Non-study Anti-*PA* Antibiotics—Controlled Trials

	CP-AI-005				CP-AI-007	
	Placebo Pooled (N = 76)	AZLI BID (N = 69)	AZLI TID (N = 66)	AZLI Pooled (N = 135)	Placebo TID (N = 84)	AZLI TID (N = 80)
All routes[a]	46 (60.5)	33 (47.8)	39 (59.1)	72 (53.3)	30 (35.7)	14 (17.5)
p-value[b]	0.3863				0.0131	
IV/Inhaled	43 (56.6)	25 (36.2)	29 (43.9)	54 (40.0)	19 (22.6)	12 (15.0)
p-value[b]	0.0221				0.2364	
Oral	30 (39.5)	19 (27.5)	24 (36.4)	43 (31.9)	21 (25.0)	9 (11.3)
p-value[b]	0.2928				0.0267	

a All routes include IV, inhaled, and oral anti-*PA* antibiotics.

b p-values are based on Fisher's Exact test and compare AZLI Pooled vs. Placebo Pooled in the CP-AI-005 study and AZLI TID vs. Placebo TID in the CP-AI-007 study

The applicant has performed a pooled analysis of the integrated results of the controlled Phase III trials. However, pooling of results from both studies cannot be considered appropriate because of the difference in the design of the studies and patient treatment profile prior to enrolment and some differences in response due to regions.

In addition a "Non-responders" analysis of integrated results is also presented for the individual disease-related outcome endpoints if they had a change from baseline of ≤ 0 in CFQ-R respiratory symptoms domain scores and FEV_1 (L), and if they had a change of ≥ 0 $\log_{10}$ *PA* CFU density in sputum. Overall non-responders were defined as no response for each of the non-missing disease-related outcome endpoints. Determinations of non-responders were not made for patients missing two or more of the three disease-related outcomes. For each of these endpoints, the AZLI BID and pooled AZLI TID and all AZLI treated patients (AZLI) were provided. Overall, the pooled AZLI group tended to have (2folds) fewer non-responders than the pooled placebo group.

Table 12: Numbers (%) of Non-responders—Integrated Phase 3 Controlled Trials (CP-AI-005 and CP-AI-007)

	Placebo Pooled (N = 160)	**AZLI BID (N = 69)**	**AZLI TID (N = 146)**	**AZLI Pooled (N = 215)**
Day 14				
CFQ-R Change from Day 0	98 (61.3)	31 (44.9)	67 (45.9)	98 (45.6)
FEV_1 Percent Change from Day 0	91 (56.9)	24 (34.8)	49 (33.6)	73 (34.0)
$\log_{10}$ *PA* CFUs Change from Day 0	60 (37.5)	29 (42.0)	34 (23.3)	63 (29.3)
Overall	41 (25.6)	6 (8.7)	18 (12.3)	24 (11.2)
Day 28				
CFQ-R Change from Day 0	98 (61.3)	30 (43.5)	69 (47.3)	99 (46.0)

	Placebo Pooled (N = 160)	AZLI BID (N = 69)	AZLI TID (N = 146)	AZLI Pooled (N = 215)
FEV_1 Percent Change from Day 0	94 (58.8)	26 (37.7)	51 (34.9)	77 (35.8)
Log_{10} *PA* CFUs Change from Day 0	66 (41.3)	20 (29.0)	30 (20.5)	50 (23.3)
Overall	47 (29.4)	10 (14.5)	20 (13.7)	30 (14.0)

Note: No response is defined as having a change from baseline ≤ 0 (CFQ-R respiratory symptoms domain, FEV_1) or ≥ 0 (log_{10} *PA* CFUs). Overall non-response defined as no response for each of the non-missing disease-related outcomes (not determined for patients missing two or more of the three disease-related outcomes).

Analysis of mean relative change in FEV_1 % predicted for patient subgroups defined by gender did not seem to reveal differences in response to AZLI therapy between male and female patients especially when focusing on the (non-pooled) results AZLI groups.

The analysis of change in mean relative change in FEV_1 % predicted for patient subgroups defined by age (6–12 years, ≥ 13 to < 18 years, < 18 years and ≥ 18 years) was compromised in study CP-AI-005 due to the very small number of patients between 6 and 12 years of age (e.g. ≤ 4 AZLI BID and placebo groups).

The results for the other age groups suggested a trend of decreasing response to AZLI BID from the age group of ≥ 13 years onwards. In study CP-AI-007, at Day 28, adults (aged ≥ 18 years; n = 58 AZLI TID), younger patients (aged < 18 years; n = 21 AZLI TID) showed an adjusted mean percent change in FEV1 of 8% and 7.5% respectively compared with 8% for adolescents (aged > 12 years to < 18 years; n = 10 AZLI) and 3.0% for children (aged ≥ 6 years to ≤ 12 years; n = 11 AZLI TID). The corresponding values for placebo treated patients were -2.4%, -2.9%, -5.4% and -8.2% respectively. The differences between AZLI and placebo treatments were significant for adults and adolescents and trended to be so in the other age categories.

The magnitude of response to TID AZLI 75 mg in patients of study CP-AI-007 was larger than that in patients on either BID or TID regimens of study CP-AI-005 with regard to pulmonary function, in respiratory symptoms, and *PA* density. In the former study there was also a region effect; at Day 28, patients in the US and Canada (n = 124: 62 AZLI and 62 placebo) showed an adjusted mean change in CFQ-R respiratory domain score of 5.89 (treatment difference vs. placebo: 7.36; p = 0.0223) on AZLI compared to 11.65 (treatment difference vs. placebo: 17.29; p = 0.0037) for patients in Australia and New Zealand (n = 39: 18 AI and 21 placebo). A similar pattern of effect was seen on the mean (adj.) change in percent change in FEV_1 (L) as for CFQ-R respiratory domain scores. The applicant suggested that seasonal differences at the time of performing the trials at the non-American and American (US) sites possibly played a role in causing the apparent regional differences in the results.

A significant reduction of PA CFU density was seen at day 28 in both placebo controlled trials (CP-AI-005 and CP-AI-007).

In CP-AI-005 reduction in PA CFU was seen earlier with TID treatment compared with BID treatment on day 14 however at day 28 the reduction was greater in BID treatment versus TID treatment. Statistically significant reduction was achieved at day 28. At Day 42 PA CFU rebounded to higher values than baseline in BID treatment than TID treatment.

In study CP-AI-007 statistical significant reduction was seen at day 14 and day 28 of treatment.

Following cessation of treatment in study CP-AI-007 at day 42 (14 days after treatment) TID treatment arm had a lower PA CFU score than placebo.

It appears that duration and magnitude of suppression of PA CFU has an effect on rebound of PA CFU density. Also, *PA* susceptibility to aztreonam seemed to impact on the magnitude and duration of response. *PA* with MIC ≤ 8 µg/mL was associated with larger reductions in *PA* sputum density than

did patients with *PA* isolates (MIC > 8 µg/mL) treated with AZLI in the Phase III placebo-controlled studies. Patients with baseline *PA* with MIC ≤ 8 µg/mL to aztreonam seemed to have better lung function response [FEV_1 % Predicted, FEV_1 (L)] than the small number of patients with baseline *PA* with MIC >8 µg/mL to aztreonam following one 28-day AZLI BID treatment course. Two weeks after AZLI therapy (day 42), the group of patients with *PA* MIC ≤ 8 µg/mL retained substantial improvement in FEV_1; however, FEV_1 dropped to below baseline levels for patients infected with *PA* MIC > 8 µg/mL. In the latter *PA* infection category, the AZLI TID regimen resulted generally in better response than the AZLI BID regimen but did not seem to result in more durable effect at day 42. Overall, based on present analysis of response to AZLI treatment in relation to baseline *PA* with MIC, no definitive correlation could be concluded.

In conclusion, pooling of results from both studies cannot be considered appropriate because of the difference in the design of the studies and patient treatment profile prior to enrolment and some differences in response due to regions.

The subgroups by age are too small to draw robust conclusions as to the age dependent performance of AZLI although in all groups there was important treatment difference between AZLI and placebo treated patients. The impact of *PA* susceptibility to aztreonam seems to be important in the management of these CF patients, although categorical analyses for the relationship between MIC and treatment response provided insufficient evidence to establish a susceptibility breakpoint for AZLI. This is reflected as such in the SPC in section 5.1. However, these issues deserve to be further confirmed in a controlled trial including at least 3 sequential courses of AZLI treatment. Such a trial is currently ongoing.

Analysis of results across studies versus Literature studies with TNS (TOBI)

Despite similar enrolment criteria, in both studies, the mean age (years) of patients was greater than that of patients enrolled in the TNS studies almost a decade ago (TNS: 21[8]; CP-AI-005: 26; CP-AI-007: 30 years of age). Additionally, the mean FEV_1 % predicted for patients in the Phase 3 placebo controlled studies was greater than that for the TNS trials (TNS: 50%[8]; CP-AI-005: 55%, CP-AI-007: 55%). The increased age and pulmonary function may be partly explained by improved treatment, including extensive use of inhaled antibiotics, like in study CP-AI-005. Of note, the primary endpoints of the TOBI-study were lung function (FEV1) and the density of *PA* in sputum at week 20 i.e. at the end of the third course of TOBI.

Roughly, the present Day 28 results with AZLI appear to be consistent with those from two TNS trials, as to the pattern of %-FEV1 improvement and decrease in the treatment off period. The smaller reduction observed between days 0 and 28 in CP-AI-005 may be attributed to the TNS treatment during the run-in phase.

Improvements in FEV1 at Day 28 (12%) were larger in the TNS pivotal registration trial (and decreased to 10% after the second and third cycle) than the values at the end of the present 1-cycle AZLI treatment. The Day 28 AZLI results from study CP-AI-007 seem to be more similar to those from the small single cycle study with TNS. Comparisons of TNS pivotal trial results with those of study CP-AI-005 may not be appropriate because of the specific feature of the latter study (extensive prior TNS use at enrolment).

In the pivotal TNS study improvements in FEV1 decreased to 8% 28 days after treatment and beginning of the second and third cycle compared to utmost 3% with AZLI TID 14 days after treatment in study CP-AI-007.

Furthermore, in the TNS pivotal registration larger trial the lung function improvement was higher in adolescents than in adults whereas the results of AZLI in this regard are inconsistent; and study CP-AI-007 did not indicate differences between these two age subgroups.

[8] BW. Ramsey, MS. Pepe et al. N Engl J Med 1999;340:23-30. “Intermittent administration of inhaled tobramycin in patients with cystic fibrosis”.

Table 13. Change in FEV_1 and *PA* CFU Sputum Density from Baseline in Published Studies

Study	*Pulmonary Function Entry Criteria*[a]	*Baseline FEV1 % Predicted (mean ± SD)*[a]	*Dose (mg)/Duration*	*FEV1 Change*	*PA Density Change (Log10)*
CP-AI-005* AZLI BID (n= 69) TID (n= 66)	FEV1 25–75%	AZLI BID 56.3 ± 14.8	75 mg BID	4%	-0.5
		AZLI TID 55.4 ± 16.2	75 mg TID	4%	-0.4
CP-AI-007 AZLI** (all) (n= 80)	FEV1 25–75%	AZLI TID 54.4 ± 13.4	75 mg TID	8%	–1.4
TNS (All)[8] (n = 258)	FEV1 25–75%	49.9 ± 15.5	300 BID/28 days	12%[b]	–2.0
Adolescents (n = 63)	FEV1 25–75%	unknown	300 BID/28 days	~16%[b]	not evaluated
Adults (n = 140)	FEV1 25–75%	unknown	300 BID/28 days	~6%[b]	not evaluated
TNS (n = 53)[9]	FEV1 ≥ 25%	55.4 ± 22.9	300 BID/28 days	7%[b]	–0.9
Colistin[5] (n = 62)	FEV1 ≥ 25%	59.4 ± 22.6	80 BID/28 days	0%[b]	–0.6

a Absolute change in FEV1 % predicted, comparison to control after 28 days of therapy
b Relative change in FEV1 % predicted, comparison to control after 28 days of therapy
* After one course of 28 days AZLI which was preceded by an initial course of TNS.
** After one course of 28 days AZLI

During the TSI phase in CP-AI-005, the improvement observed in patients measured by FEV1 was lower than that observed in the early TSI trials. The mechanism for the decreased response is not clear since the MICs for TSI observed in this trial were similar to those observed historically.
[In the pivotal TNS study an interim analysis of a subgroup of 128 patients treated with this regimen for 11 months has shown that the improvement in lung function is maintained (increase in FEV1 at week 44 as compared with week 0, 9.8 percent; data not shown)].

Long term exposure data are not available from the placebo-controlled trials with AZLI.

In conclusion, the comparisons between AZLI studies are difficult to interpret because of the specific feature of study CP-AI-005 i.e. extensive prior TNS use at enrolment in contrast to CP-AI-007. The latter study is also more amenable for comparison with the pivotal TNS registration trial and the small single cycle comparative trial with TNS vs. colistin inhalational.

Comparison of the results of CP-AI-007 with those of the pivotal TNS registration trial seems to be in favour of TNS with respect to %-FEV1improvement and durability of this effect during the treatment off period. As to the pattern of improvements by age category the results of AZLI in this regard are inconsistent; moreover, study CP-AI-007 did not indicate differences between adolescents and adults in contrast to the higher response in adolescents than in adults in the TNS pivotal registration trial. However, the subgroups by age are too small to draw robust conclusions as to the age dependent performance of AZLI.

Overall, the most appropriate way to compare the clinical results of the recommended dosage of AZLI with the approved TNS is a head to head randomised comparative study in a larger group of patients for the duration of 3 treatment cycles. Such a study is presently ongoing. Such a study will also

[9] Hodson ME, Gallagher CG, Govan JR. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. Eur Respir J 2002;20(3):658-64

neutralise any effects such as tolerance to TNS (as in study CP-AI-005) or potential seasonal effects (as in study CP-AI-007 versus CP-AI-005).

- Clinical studies in special populations

No special studies were provided. In the present main clinical trials, pulmonary function response was comparable for AZLI-treated patients of all studied age groups.

- Supportive studies

CP-AI-006: A Phase 3, Open-label, Follow-on Study of Multiple Courses of Aztreonam Lysinate for Inhalation (AZLI) in Cystic Fibrosis Patients (AIR-CF3).

The primary objective of the study is to evaluate the safety of repeated exposure to AZLI in cystic fibrosis (CF) patients. Secondary objectives include evaluation of the effects of repeated exposure to AZLI on disease-related endpoints and microbiology.

Follow-on study CP-AI-006 eligible patients from the two randomized trials (CP-AI-005 or CP-AI-007) received AZLI with the PARI eFlow Nebuliser at the same regimen to which they had been previously assigned and the same key efficacy variables were measured. As of the data cut off for this summary, 207 patients have been treated with AZLI in the open label follow-on trial. Baseline data suggest heterogeneity of the different subgroups (from placebo worse than from AZLI previous treatment) with regard to baseline disease severity. Pooled results are not useful.

Furthermore, in this open-label trial, there were no protocol restrictions on use of non-study drug antibiotics. During the study, patients may be treated as needed with any anti-*PA* antibiotics (oral, IV, or inhaled), with the exception of IV aztreonam therapy for any duration. Some patients were put on continuous alternating therapy with other inhaled antibiotics. The proportion of patients in the AZLI BID group who used non-study anti-*PA* antibiotics by IV/inhalational route was approx 71% and equal to that in the pooled AZLI TID group.

Most frequently used other antibiotics were: 54 (66%) and 85 (68%) patients who used azithromycin in the total BID and TID groups, respectively; 56 (68%) and 77 (62%) patients who used tobramycin in the total BID and TID groups, respectively and finally 44 (54%) and 66 (53%) patients who used ciprofloxacin in the total BID and TID groups, respectively.

There were 17 patients who enrolled in the CP-AI-005 study who received at least one dose of TSI, but discontinued during the TSI phase, and thus never received placebo or AZLI.

Generally, better responses were reported in patients treated with AZLI TID for CFQ-R (respiratory domain scores) mean and categorical changes compared to that of the AZLI BID group for the first three treatment courses in the open phase. Mean relative change in FEV_1 % predicted showed a similar pattern of change. Similarly**,** reductions in *PA* CFU density summarised by previous study seemed to indicate better results in patients the AZLI TID regimen.

During the first three treatment courses, the percentages of patients starting tobramycin treatment in any visit interval were similar for both regimens with no apparent relationship between on- and off-treatment cycles (maximum approx. 20% in the AZLI TID group who received AZLI TID in the controlled trial versus approx. 31% in the AZLI BID group who received AZLI BID in the controlled trial).

Other supportive data.

The applicant designed the open uncontrolled study **CP-MCID-001** to evaluate the CFQ-R by determining the minimal clinically important difference (MCID) score in children and adolescents/adults with cystic fibrosis (CF) and chronic *PA* infection who received TOBI for their symptoms. Patients were allowed to take other anti-*PA* agents. Correlation of change in clinical

symptoms as measured by the CFQ-R with change in pulmonary function and with the GRCQ was also analysed. The magnitude of improvement in respiratory symptoms, as measured by responses to the GRCQ-Respiratory, was used to categorize patients as to whether they had experienced minimal, moderate, large, or no changes in respiratory symptoms during TNS treatment. 66 patients were enrolled in the study: 23 children and 43 adolescents or adults. The mean age was 17.9 years (range 5–48 years). No data were collected to measure treatment compliance in this study.

The **TNS phase of CP-AI-005** was also similarly designed. In both studies, MCID estimates were based on data obtained before and after 28 days of treatment with TNS.

In study **CP-MCID-001** forty three (65%) patients completed the study: 17 children and 26 adolescents or adults. Patients had acute symptoms of CF; at baseline, the mean FEV1 % predicted was 65.1%. Mean changes from baseline in the CFQ-R were positive overall in adolescents/adults ≥ 18 years old compared with negative changes in patients 14 to < 18 years old. In the respiratory domain, however, the combined children/adolescent group < 18 years old had greater mean positive changes from baseline in the CFQ-R at Visit 2

On the combined data from children, adolescents, and adults, the MCID for the respiratory symptoms domain was 11.6 and the MCID for the physical functioning domain was 10.3. Scatter plots of correlations between changes in the CFQ-R, the GRCQ, and FEV1 showed that results of the variables were modestly correlated (R=0.4571).

The correlation of the change in CFQ-R versus the change in FEV1 % at Visit 2 by baseline FEV1 % predicted for the combined children/adolescents/adults was calculated. It was moderately correlated for patients with < 75% baseline FEV1 % predicted (R = 0.5438), but not correlated for patients with ≥ 75% baseline FEV1 % predicted (R = 0.0291).

In study **CP-AI-005** in the TNS phase in patients completing a 28-day course of TSI there was on average no improvement in clinical symptoms as measured by the respiratory domain of the CFQ-R.

In the controlled phase of the study the correlations between percent change in FEV1 and actual change in CFQ-R respiratory domain scores were poor in the AZLI BID, AAZI TID and pooled placebo groups (correlation coefficient = 0.33, 0.24, and 0.33 for AI BID, AI TID, and pooled placebo, respectively). It suggested that change in CFQ-R respiratory domain score increased as percent change in FEV1 increased in all treatment groups.

In both studies, MCID estimates were based on data obtained before and after 28 days of treatment with TSI. The MCID for the CFQ-R respiratory domain was approximately 11 in CP-MCID-001 and 5 in the TSI phase of CP-AI-005. This difference was attributed to the different baseline respiratory status of the patient groups; patients in CP-MCID-001 were experiencing symptoms predictive of exacerbation at the time of enrolment, whereas those in CP-AI-005 were stable at enrolment. Accordingly, the FDA and the sponsor agreed that the MCID estimate of 5 was the most appropriate standard for the patient population in CP-AI-007.

In conclusion, the exploratory results of CP-MCID-001 should be interpreted with caution because of the uncontrolled design of the study and the very limited number of patients and distribution over the different age and disease severity categories. Furthermore, compliance was not evaluated in the study. In the larger study population of study CP-AI-005 in the TNS phase of there was on average, in patients completing a 28-day course of TSI no improvement in clinical symptoms as measured by the respiratory domain of the CFQ-R whereas in the controlled phase of the study the correlations between percent change in FEV1 and actual change in CFQ-R respiratory domain scores were poor in the AZLI BID, AZLI TID and pooled placebo groups (correlation coefficient = 0.33, 0.24, and 0.33 respectively).

The CFQ-R results suggest that they can be used only to obtain supportive measurement of the impact of the antibiotic inhalational therapy on respiratory domain scores but there is poor to modest correlation between the changes in the CFQ-R with changes in FEV1 percent predicted. The

usefulness CFQ-R as a quantitative tool to measure in a standardised fashion meaningful clinical change and to be used as discriminatory endpoint in controlled comparative clinical trials needs to be validated appropriately. This is, however, beyond the scope of this MAA.

- Discussion on clinical efficacy

Overall, the observed improvements in pulmonary function and PA CFU density obtained with AZLI at day 28 in both placebo-controlled short-term studies CP-AI-005 and CP-AI-007 favour the efficacy of the recommended 28 days course of AZLI 75 mg TID above placebo, although the superiority of AZLI 75 mg TID above AZLI BID was not convincingly demonstrated in the former study. The design of study CP-AI-005 and the chosen extensively pre-treated population might not have been the appropriate choice to detect convincing differences between the BID and TID AZLI regimens. Of note, the power of the Phase II trial CP-AI-003 to detect relevant differences between active treatments and placebo was compromised (too small number of evaluable patients and the mild to moderate CF disease severity as approx. 80% had FEV1 ≥ 60% of predicted). However, the rationale for choosing TID 75 mg for AZLI to obtain a better antibacterial coverage with AZLI can be supported on the basis of microbiological results. Pooling of results from both Phase III studies cannot be considered appropriate because of the difference in the design of the studies and patient treatment profile prior to enrolment and some differences in response due to regions explained by the applicant by being possible seasonal effects.

Generally, the magnitude of observed lung function and *PA* CFU density improvements in the less extensively TNS pre-treated (no dornase and no oral azithromycin allowed) population of trial CP-AI-007 were larger than in the extensively pre-treated population of trial CP-AI-005. The observed effects within AZLI patients in the latter study should be considered as the resultant of the initial TNS course, concomitant dornase and AZLI course. Furthermore, this pre- and co-medication might have narrowed the room of improvement in the patients of the latter study compared to the patients in study CP-AI-007.

The magnitude of improvement in lung function in patients in the more severe disease category (FEV1 ≤ 50% of predicted) was importantly smaller than that in patients in the less severe disease category (FEV1> 50% of predicted). In both studies, the observed responses diminished importantly within 2 weeks after cessation of the AZLI treatment. This raises concerns on the durability of clinical response to AZLI.

Similar patterns of effects were also noted for CFQ-R, mean (adjusted) change in respiratory symptoms at Day 28. Of note, however, the rather high categorical placebo response with improved score in 37 % of patients versus 52-56% in the AZLI groups in both studies and decreasing to 30% and 45% at day 42 in study CP-AI-007. In both studies the correlations between percent change in FEV_1 and actual change in CFQ-R respiratory domain scores were poor in the AZLI and placebo groups (see comment below with regard to the clinical relevance of this new evaluation tool).
As expected the median time to need of inhaled or IV antibiotics due to pre-defined symptoms (measured from Day 0) was longer in the AZLI treated patients than in the placebo treated patients.

Robust conclusions as to the age dependent performance of AZLI cannot be drawn as subgroups by age were very small, although in all groups there was important treatment difference between AZLI and placebo treated patients. The numbers of children 6-12 years of age were too small to allow provisional meaningful conclusions. The impact of *PA* susceptibility to aztreonam seems to be important in the management of these CF patients, although categorical analyses for the relationship between MIC and treatment response provided insufficient evidence to establish a susceptibility breakpoint for AZLI.

The present results in the rather small subgroups of patients are also difficult to compare with those of the pivotal efficacy study for TOBI which included larger groups of patients (as to gender, age, and disease severity) and for the duration of 3 treatment cycles. Because of the specific feature of study CP-AI-005 i.e. extensive prior TNS use at enrolment, study CP-AI-007 is more amenable for comparison with the pivotal TNS registration trial. The latter comparison seemed to favour TNS with

respect to %-FEV1improvement and durability of this effect during the treatment off periods. As to the pattern of improvements by age category study CP-AI-007 did not seem to indicate differences between the small groups of adolescents and adults in contrast to the higher response in adolescents than in adults in the TNS pivotal registration trial. However, historical comparisons between different studies should be interpreted with caution as differences in the management of patients in the different periods of the trials and differences as to enrolled populations and durations (and seasons in which they were performed) of trials cannot be accounted for appropriately. The most appropriate way to compare the clinical results would be in a head to head randomised fashion for the duration of 3 treatment cycles comparing the definitively recommended dosage of AZLI with the approved TNS in a larger group of patients.

Open uncontrolled follow-on study CP-AI-006 is not useful to draw appropriate conclusions due to the design, heterogeneity of the populations and used interfering co-medications. Reported results, not totally unexpected, seem to be more favourable for the AZLI TID regimen. Appropriate conclusions with regard to the durability of response cannot be drawn.

Finally, the CFQ-R results suggest that they can be used only to obtain supportive measurement of the impact of the antibiotic inhalational therapy on respiratory domain scores but there is poor to modest correlation between the changes in the CFQ-R with changes in FEV1 percent predicted. The usefulness CFQ-R as a quantitative tool to measure in a standardised fashion meaningful clinical change and to be used as discriminatory endpoint in controlled comparative clinical trials needs to be validated appropriately. This is, however, beyond the scope of this Marketing Authorisation Application.

Clinical safety

- Patient exposure

In the present submission a total of 373 patients have received at least one dose of AZLI in the Phase 2/3 studies, 278 of these 373 patients (74.5%) had been treated with AZLI for a total of at least 28 days. In Study CP-AI-006, 145/207 patients (70%) had been treated with AZLI for > 84 days (the equivalent of three 28-day courses) and 55 patients (27%) had been treated for >168 days (the equivalent of six 28-Day courses)

Sputum and plasma concentrations of aztreonam have been monitored in several clinical studies of AZLI.

Like for other inhalational antibiotic therapies in the management of chronic *PA* infections in CF patients AZLI treatment causes minimal systemic exposure; plasma concentrations of aztreonam from administration of AZLI by inhalation have been shown to be approximately 80- to 300- fold lower than peak plasma concentrations following intravenous administration of 0.5- and 2-gram therapeutic doses of aztreonam. Consequently, AZLI associated AEs were as expected of low frequency.

- Adverse events

The majority of patients in both the placebo and AZLI treatment groups experienced at least one AE of any causality. Drug-related AEs were reported by a higher proportion of patients treated with AZLI in both studies (table 14).

Table 14. Summary of AEs: Individual and Integrated Studies CP-AI-005 and -007

Patients Reporting AEs	**Placebo** Pooled (n = 160) n (%)	**AZLI** CP-AI-005 75 mg BID (n = 69) n (%)	CP-AI-005 75 mg TID (n =66) n (%)	CP-AI-007 75 mg TID (n = 80) n (%)	CP-AI-005 and -007 75 mg TID (n = 146) n (%)
Any AE	136 (85.0)	62 (89.9)	61 (92.4)	63 (78.8)	124 (84.9)
Drug-related AE[a]	42 (26.3)	18 (26.1)	20 (30.3)	28 (35.0)	48 (32.9)
SAE	15 (9.4)	6 (8.7)	7 (10.6)	5 (6.3)	12 (8.2)
Drug related Cough[a]	<10%	13%	14%	19%	16.4

a) Drug-related AEs are those with a causality of possible or probable.

In Study CP-AI-003, there was a possible dose-related trend in the incidence of drug-related cough (14% AZLI 75 mg vs. 19% AZLI 225 mg vs. 10% placebo). This is explained by the applicant as being partly due to airway reactivity. Integrated data for the Phase II/III placebo-controlled studies showed (based on measurements of FEV_1 taken pre-dose and 30 minutes following study drug administration) that a small percentage of patients had declines of ≥ 15% in FEV_1. After the first dose of study drug on Day 0, 2% of pooled AZLI patients and 3% of placebo patients had declines of ≥ 15% in FEV_1. Lower percentages of patients had declines of ≥ 15% in FEV_1 at subsequent time points. Of note, all patients in the placebo controlled phase II trials were on bronchodilator co-medication.

Overall, cough was the most frequent drug related AE in the controlled Phase III studies and was reported at higher rate by the AZLI treated patients (approx. 16 % in the pooled AZLI TID) than by the placebo treated patients (<10%). The cough in the AZLI treated patients was associated with airway irritation leading to cough, onset of cough occurred commonly immediately after administration of the first dose of AZLI whereas in the placebo group it did not occur on the day of study drug administration.

Other less common drug related AEs in the pooled AZLI TID group in the controlled Phase III studies were chest discomfort and wheezing which occurred at a rate of approx. 3% followed dyspnoea, throat irritation, pharyngolaryngeal pain and productive cough at a rate of approx. 2%. Several of these AEs increased slightly in the open-label follow-on study CP-AI-006. Furthermore, additional dug related AEs were reported such as hemoptysis (7%), respiratory tract congestion (3%), nasal congestion (2%), rash (1%), rhinorrhea (2%), fatigue (2%), and arthralgia (2%).

In the open study, cough was the most common drug-related AE for all AZLI treatment courses, but the incidence rate generally decreased by treatment course. In treatment courses 1, 2, and 3, the total incidence of drug-related cough was 11.6%, 5.9%, and 3.6%, respectively. The incidence rate was similar in the BID and TID regimens for each treatment course.

Microbiological effects.

In both placebo controlled Phase III studies CP-AI-005 and -007) at Day 0 comparable percentages of patients in the treatment groups had positive culture results for *PA* (which was an inclusion criterion) with slightly broader ranges in study CP-AI-005 namely 97% in the placebo group vs. 89% in AZLI BID and 97% in the AZLI TID group; in study CP-AI-007 95% in the AZLI TID group and 94% in the placebo group. A minority of the patients had also positive cultures for other pathogens.
In study CP-AI-005 at Day 0 higher percentages (≤15%) of patients had positive cultures for *S. maltophilia* and *A. xylosoxidans* than in study CP-AI-007 (< 2% in the AZLI group). In study CP-AI-007 the percentages of patients with *S. maltophilia* and *A. xylosoxidans* isolated at Day 0 were lower in the AZLI group (1.4% for both micro-organisms) than in the placebo group (4.9% and 6% respectively).
In both studies, AZLI groups at Day 0, higher percentages (42-50%) of patients had positive cultures for *S. aureus* than the placebo groups (32-37%).

Since patients with *B. cepacia* were to be excluded there was only 1 patient with positive culture for *B. cepacia* at day O, namely 1 (1.4%) in the AZLI group in study CP-AI-007.

At Day 28 of treatment there were slight decreases in the % of patients with positive cultures for *PA* in the AZLI groups and rise again to at least baseline values at Day 42. Such a decrease is not expected for suppressive therapy and the presence or absence of *PA* is more likely to be attributable to variations in sampling technique, or to the patients' ability to produce sputum, than to the disappearance of *PA* in individual patients.

In the very small numbers of patients with positive cultures for *S. maltophilia* and *A. xylosoxidans* no clear effects of treatments through day 42 compared to baseline values were observed. In the relatively high proportions of patients with positive cultures for *S. aureus* no clear effects of treatments through day 42 compared to baseline values were observed across the studies. A trend to an increase in the proportion of positive cultures in the AZLI TID in study CP-AI-005 at day 42 was not observed in the AZLI TID group in study CP-AI-007.

In studies CP-AI-005 and -007, MIC50 and MIC90 of aztreonam for all *PA* isolates generally remained unchanged for all treatment groups at Day 28 through Day 42 (and 56 in study 007).

For *PA* isolates with the highest MIC from each patient, the percentages of patients who had increases in their highest aztreonam MICs were notably higher in the AZLI BID and TID groups than in the placebo groups at all time points. In study CP-AI-005 at Day 28 37-38% patients in the AZLI groups had an increase in their highest MICs, compared with 21% patients in the pooled placebo group. The increase in MICs during treatment trended to revert in the treatment free period. The percentage of patients whose *PA* isolate with the highest MIC of aztreonam was above the parenteral breakpoint (> 8 µg/mL) increased from Day 0 to Days 14 and 28 in the pooled AZLI group, but not in the pooled placebo group whereas at Day 28 the proportions of patients with increases reached 43-44% patients in the AZLI groups compared with 27-33% patients at Day 0. The percentages tended to revert in the treatment free period (clearest being within the AZLI TID group) and percentages returned to near-Day 0 values after Day 56.

Apart from transient changes, there seemed to be no notable increases in the MIC50 or MIC90 of any of the other antibiotics tested after treatment with AZLI (tobramycin, gentamicin, amikacin, piperacillin, cefepime, meropenem, ceftazidime, ciprofloxacin, and ticarcillin/clavulanate).

In the open follow-up uncontrolled study CP-AI-006**,** the pattern of effects was similar to that in the original controlled studies. There was no consistent trend in the percentage of patients with the highest MIC over the time interval during the first three treatment courses. The MIC data collected at additional patient visits beyond the third treatment course suggested that the susceptibility of *PA* to aztreonam may decrease more readily over time with BID than TID dosing.
There were no notable increases in the MIC50 or MIC90 of any of the other antibiotics tested against *PA* after treatment with AI.

Furthermore, nearly half of all patients in the study had at least one positive culture for *Aspergillus spp.* during study participation, whereas three patients were prescribed concomitant medications to treat *Aspergillus* infections.

- Serious adverse event/deaths/other significant events

SAEs. Overall reported SAEs for the pooled placebo and pooled AZLI groups occurred generally at similar rates; higher rates in the AZLI treated patients included chest discomfort (< 1% AZLI vs. 0% placebo), pulmonary function test decreased (2% AZLI vs 1% placebo) and wheezing (1% AZLI vs. 0% placebo). Four patients experienced SAEs that were considered by the investigator to be related to AZLI (in study CP-AI-006: 1 rash, 1 cough and productive cough, 1 cough, productive cough and dyspnea, 1 arthralgia and joint swelling).

Deaths. No patients died during the placebo-controlled studies. One patient in Study CP-AI-006 died (mainly due to massive hemoptysis and cardiac arrest) after completing eight courses of AZLI. All events of hemoptysis, and all other AEs experienced by the patient during the periods of hospitalization, were considered by the investigator to be unlikely to be related to study drug). Multi-drug resistant *P. aeruginosa* was cultured from the patient at baseline of the open-label study, but no treatment-related resistance to aztreonam was observed. In Study CP-AI-006, the highest aztreonam MIC values recorded were 128 µg/mL at the earliest visit and 256 µg/mL at the latest visit; transient increases to 512 µg/mL were observed at the end of treatment courses one and four.

The applicant should discuss the place of AZLI in the treatment of CF patients in the sought indication with documented multi-drug resistant *P. aeruginosa*. This should be monitored in the ongoing comparative study versus TNS and the open follow-up study CP-AI-006.

- Laboratory findings

In the Phase II/III studies with AZLI substantial variability in laboratory profiles were observed.
There were no drug related ARs associated with changes in serum chemistry variables either in the placebo-controlled or the open uncontrolled follow on study.

Mean counts for WBCs, particularly neutrophils, were generally at the high end of the respective reference ranges for all treatment groups, consistent with a diagnosis of CF. Reductions in white blood cell and neutrophil counts were observed for AZLI-treated patients in integrated analyses of the placebo-controlled studies but the differences between AZLI and placebo treated patients were small.
The pattern of shifts from baseline to outside the normal range for hematology variables in the AZLI treated patients was similar to that in the placebo treated patients. There were no drug related hematology results reported as AEs in the placebo-controlled studies.

In the open uncontrolled study CP-AI-006, a similar pattern was observed.

- Safety in special populations

Gender. In the placebo-controlled studies, the overall incidence of specific AEs was generally higher in females compared with males, however, there were generally no notable differences between treatment groups (AZLI vs placebo) with some exceptions in increases for e.g :

- the proportions of patients with chest discomfort (respiratory disorders SOC) were for female AZLI-treated patients 8% vs. 2% in those on placebo; incidence of cough in female patients (59% AZLI vs. 46% placebo), nasal congestion in females (18% AZLI vs. 14% placebo), pharyngo-laryngeal pain in male patients (11% AZLI vs. 6% placebo), pyrexia was reported with a higher incidence in AZLI-treated patients of each gender subgroup (9% AZLI vs. 4% placebo for males; 14% AZLI vs. 8% placebo for females), rhinorrhea female patients (14% AZLI vs. 7% placebo) and wheezing (18% AZLI vs. 8% placebo).

- in the open-label study CP-AI-006 proportions of drug-related AEs reported were 35% for both genders and drug-related AE by regimen (31% male vs. 29% female for BID; 37% male vs. 39% female for TID).

Age. A good comparison of the AE profiles by age groups is hampered because of the rather small numbers of patients enrolled into the Phase II/III clinical trials with AZLI and especially the very limited number of children; the distribution of patients by age was: 77% adults, 18% adolescents (age 13 to < 18 years), and 5% children (age 6 to 12 years).

In the placebo-controlled studies, the incidence of many selected AEs was higher among patients ≥ 18 years of age, consistent with the general observation of increased disease severity in adult CF patients. However, some events were observed in a higher overall proportion of paediatric patients (age < 18 years) treated with AZLI e.g. pyrexia was observed in 18% of paediatric patients vs. 9% of adults; the differences between treatment groups (AZLI vs. placebo) was only notable for patients in

the age category < 18 years as no events were reported in the corresponding placebo group. Generally the differences between treatment groups (AZLI vs. placebo) for adults and children (age < 18 years) were not notable.

In conclusion, the very limited number of children hampers the appropriate comparison of safety profile of AZLI by age. More experience in children is required and hopefully this will become available from the ongoing comparative phase III study.

Race. Approximately 94% of patients treated with AZLI have been Caucasian consistent with data (95%) on genetics of CF disease. No conclusions can be drawn about the potential influence of race on the safety profile of AZLI in CF patients.

Baseline disease severity. As expected, among patients treated with AZLI, the incidence of most respiratory symptoms and other AEs was lower in the subgroup of patients with baseline FEV_1 % predicted > 50%. Generally the differences between treatment groups (AZLI vs. placebo) by disease severity category were not notable with some exceptions most importantly e.g. for:
Nasal congestion occurred at a higher incidence among AZLI-treated patients in the subgroup of patients with FEV_1 % predicted ≤ 50% (24% AZLI vs. 8% placebo).

For chest discomfort (respiratory disorders SOC) a higher incidence was observed among AZLI-treated patients (7% AZLI vs. 2% placebo) for the subgroup of patients with FEV_1 % predicted > 50%. Pyrexia occurred with a higher incidence (16% AZLI vs. 9% placebo for patients with FEV_1 % predicted ≤ 50%; 9% AZLI vs. 4% placebo for patients with FEV_1 % predicted > 50%) in the AZLI groups of both disease severity categories.

Renal and Hepatic Function. Renal and hepatic AEs are of particular interest since aztreonam is cleared mainly by renal route and reports of elevations of AST, ALT, and alkaline phosphatase and hepatitis and jaundice with an incidence of less than 1% after IV administration of aztreonam have been reported.

In Phase III clinical studies with AZLI patients were excluded from participation if they had abnormal renal or hepatic function, defined as creatinine > 2 times upper limit of normal range (Studies CP-AI-005 and -007) and AST or ALT > 5 times upper limit of normal range (Studies CP-AI-005, -007, and -006).

As expected, given the low systemic concentration of AZLI after inhalation, clinically relevant changes in renal and hepatic laboratory results were not observed in Phase II/III trials.

Extrinsic factors. The overwhelming majority of the patients in the Phase II/III were enrolled in US centres. Only in study CP-AI-007 39 patients (18 AZLI and 21 placebo) were treated in Australia and New Zealand besides the 125 patients (62 AZLI and 63 placebo) in the US and Canada.
A greater percentage of patients in the AZLI group in the US and Canada reported at least one drug-related AE (39%) compared with either the placebo group in the US and Canada (24%) or in Australia and New Zealand (22% AZLI and 19% placebo). The applicant considers the regional seasonal differences observed in Study CP-AI-007 as possible explanation for the observed difference as almost half the patients were enrolled within the last five months of the trial, corresponding to fall and early winter in the northern hemisphere and spring and summer in the southern hemisphere.

- Immunological events

There were no immunological events reported in the Phase II/III studies except for some non severe allergic reactions at a low rate despite the fact that a small number (18-26% of the patients in the different studies) had pre-existing allergy to beta-lactams.

Three of the 373 patients who have received at least one dose of AZLI were discontinued from study due to possible allergic reactions : 1 case due to urticaria, rash and dizziness; 1 case due to serum sickness symptoms (arthralgia, multiple joint swelling, peripheral edema, musculoskeletal pain); and

1 case of pulmonary exacerbation, SAE rash (diffuse rash on face) and AEs of chest discomfort, throat tightness, and swelling face (symptoms resolved after antihistaminic and corticosteroid treatment, had documented pre-existing beta-lactams allergy).

For several of the reported AEs among patients treated with AZLI in the Phase III placebo-controlled studies, there were differences between the beta-lactam allergy subgroups e.g. for cough, dizziness, rash and throat irritation. However, these comparisons should be interpreted with caution, as the numbers of patients are small.

Relevant precautions and warnings are mentioned in the proposed SPC for patients with known beta-lactam allergy.

- Safety related to drug-drug interactions and other interactions

No formal drug interaction studies were conducted during the AZLI clinical development programme. Exploratory analyses of the potential effects of relevant concomitant medications on AEs in the Phase II/III clinical trials were provided. *Bronchodilator* was used in all patients in the placebo- controlled Phase III studies whereas *Dornase alfa* was used by 72% of patients in the Phase II/III clinical trials.

There were no clinically relevant adverse interactions between these agents and AZLI. This holds also for *pancreatic enzymes* (used by 89% of patients in the Phase II/III clinical trials), and *oral and/or inhaled corticosteroids* (used by 61% of patients in the Phase II/III clinical trials).

Concomitant *azithromycin* usage as in Study CP-AI-005 (72% AZLI vs. 66% placebo) was associated with a higher incidence of some respiratory symptoms (e.g., hemoptysis [16% vs. 8%, for the without azithromycin subgroup], nasal congestion [24% vs. 13% resp.], and respiratory tract congestion [21% vs 5% resp.]). In general, the same pattern was not observed when placebo patients were compared between the azithromycin subgroups.

Concomitant tobramycin (IV or inhaled) usage as in study CP-AI-006 (65% of patients have used that at least once to date) was associated with a higher incidence of e.g. chest discomfort (22% vs. 11% without tobramycin for the respiratory disorders SOC), cough (90% vs. 66% without tobramycin), hemoptysis (30% vs. 16% without tobramycin), nasal congestion (40% vs 13% without tobramycin), pyrexia (43% vs. 12% without tobramycin), rash (10% vs. 1% without tobramycin) and wheezing (24% vs. 10% without tobramycin).

Relevant precautions and warnings in the light of above mentioned findings were not mentioned in the proposed SPC.

- Discontinuation due to adverse events

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, arthalgia or hemoptysis.

Pregnancy. Female patients of childbearing potential who enrolled in studies of AZLI were required to practice an acceptable method of birth control and could not be lactating. However, a positive pregnancy test was reported for one patient in Study CP-AI-006. This patient was discontinued from the study; the pregnancy is ongoing.

- Post marketing experience

No post-marketing data are available for Aztreonam Lysine 75 mg Powder for Nebuliser Solution.

- Discussion on clinical safety

Overall**,** the adverse events (AEs) profile of AZLI gives no reasons for concerns after short-term single course treatment with AZLI. Cough was the most frequent drug related AE in the controlled Phase III studies which was associated with airway irritation. Despite BD use, cough was reported at higher rate by the AZLI treated patients (approx. 16 % in the pooled AZLI TID) than by the placebo treated patients (<10%). Cough seemed to be less reported after repeated courses with AZLI in the open follow-up uncontrolled study CP-AI-006. The seasonal explanation given by the applicant with regard to certain AEs is plausible; hopefully the ongoing comparative phase III study will shed more light on this issue.

Furthermore, the very limited number of children hampers the appropriate comparison of safety profile of AZLI by age. More experience in children is required and hopefully this will become available from the ongoing comparative phase III study.

The microbiological effects after treatment with AZLI suggested an increase in the frequency of positive culture for *S. aureus* which seemed to revert to baseline values in the treatment free period.
In studies CP-AI-005 and -007, MIC50 and MIC90 of aztreonam for all *PA* isolates generally remained unchanged for all treatment groups at Day 28 through Day 42. For *PA* isolates with the highest MIC from each patient, use of aztreonam seemed to induce increases in their highest aztreonam MICs above that of placebo this was also reflected in the results for patients with the highest MIC of aztreonam was above the parenteral breakpoint (> 8 μg/mL). The increases tended to revert in the treatment-free period. In the open follow-up uncontrolled study CP-AI-006**,** the pattern of effects was similar to that in the original controlled studies. Furthermore, nearly half of all patients in the study had at least one positive culture for Aspergillus spp. during study participation, although three patients were prescribed concomitant medications to treat Aspergillus infections. These observations need to be confirmed in the ongoing phase III controlled study with AZLI versus TNS (during 3 courses). In addition, it is of interest also to document the long-term potential of AZLI to select AZLI resistant *PA* (with phenotypic and genotypic characterisation) and for colonisation and superinfection with *S. pneumoniae*, *Candida* and *Aspergillus species*.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is not considered to be acceptable. There are some outstanding issues regarding the quality of the active substance and the finished product, which need further clarification.

Non-clinical pharmacology and toxicology

Both in rat and dog studies, no significant systemic toxicities were encountered. However, partly reversible irritancy effects in the upper respiratory tract were shown. Although effects are mild, and restricted to the upper airways, clinical relevance cannot be ruled out with certainty.

In addition, in high dose, the incidence of C-cell adenomas in the thyroid gland was increased in female rat. Considering the increasing life expectancy especially for young patients and considering the fact that only one carcinogenicity study has been performed with aztreonam, it is still necessary to address the relevance of C-cell adenoma in this specific situation.

Efficacy

The present short-term efficacy results obtained after a single course of Cayston 75 mg TID are encouraging. However, the durability of the improvements in the treatment-off periods is not sufficiently demonstrated. Furthermore, robust conclusions as to the age dependent performance of Cayston cannot be drawn as subgroups by age were very small, although in all groups there was important treatment difference between Cayston and placebo treated patients. The numbers of children 6-12 years of age were too small to allow provisional meaningful conclusions. Appropriate evaluation of efficacy and durability of response across different age groups and disease severity in the targeted CF population with the chronic infectious (*PA*) condition requires randomised trials during at least 3 courses of the inhalational antibiotic.

Safety

The adverse event profile observed in the Cayston trials has been dominated by respiratory adverse events and appears consistent with the expected signs and symptoms of the patients' underlying CF lung disease. The adverse reactions attributable to Cayston were primarily self-limiting, local effects associated with inhalation of the proposed medicinal product. However, the long-term significance of these findings has not been determined. There were no serious allergic reactions and few SAEs associated with Cayston.

The present safety data are insufficient to resolve the raised concerns with regards to the risk of acquired resistance.

The current clinical safety data for Cayston from clinical studies submitted is considered as limited, in particular for children. It is acknowledged that further clinical studies are ongoing which, when available will provide additional safety information and long-term safety data in particular, but this is currently lacking.

- User consultation

The user testing report submitted is adequate and in accordance with current recommendations.

Assessment of requirements for granting a Conditional Marketing Authorisation

All four requirements in Article 4 of Commission Regulation (EC) 507/2006 need to be satisfied, i.e.:

1. It fulfils an unmet medical need,
2. It is likely that the applicant will be in a position to provide the comprehensive clinical data,
3. It has a positive Risk Benefit Analysis, and
4. The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Applicant's position

It is argued by the applicant that AZLI meets the unmet need in CF patients infected with PA in three ways:

1. Aztreonam's mechanism of action is different from that of aminoglycoside antibiotics and thus its use should not contribute to the emergence of aminoglycoside-resistant strains of PA.
2. Aztreonam is active against aminoglycoside- and multidrug-resistant PA and may have activity against several other CF pathogens with intrinsic resistance to tobramycin, including B. cepacia.
3. Aztreonam does not cause ototoxicity and nephrotoxicity, which are side effects associated with aminoglycosides.

Furthermore, the applicant asserts that in comparison to currently available therapies, AZLI provides the following significant benefits to CF patients with PA:

- A significant improvement in lung function in comparison to placebo. AZLI also demonstrates the ability to improve lung function in TOBI experienced patients.
- Increased quality of life as a result of the improvement in lung function.
- A statistically significant delay in the time to need for intravenous (IV) antibiotics.
- A rapid mode of administration (via the eFlow Nebuliser device) thus reducing patients' treatment burden.
- A less disrupted lifestyle due to the small, portable eFlow Nebuliser device, which potentially allows patient to live a more normal life.
- A safe and well tolerated product.
- No decrease in the susceptibility of PA to aztreonam or other antibiotics, including betalactams, aminoglycosides, and quinolones, and no concerning trends in the treatment emergent isolation of other bacterial pathogens over three treatment courses of AZLI administered TID (28 days on, 28 days off).

Reference is also made to the fact that AZLI received designation as an orphan medicinal product and as such is intended for either "treatment, the prevention, or the medical diagnosis of a seriously debilitating disease or life-threatening disease".

During the procedure (responses to Day 120 & 180 List of Questions/ Outstanding Issues), the applicant stated that sufficient efficacy and safety data are provided to support a positive risk-benefit assessment for granting a Conditional MA, confirmed with external results from a case-matched control population.

CHMP's position

It is known that there are very limited available effective options for inhalational anti-pseudomonal antibiotic therapy in CF patients with chronic PA infection and in principle AZLI might offer an additional possibility in this field, with a different resistance profile than the presently established inhalational tobramycin therapy in the target population. However, this has to be demonstrated.

The requirements as laid in Article 4 of the Commission Regulation (EC) No 507/2006 on the Conditional MA for medicinal products for human use, falling within the scope of Regulation (EC) No 726/2004 have not been fulfilled with the present data. In particular, a positive Risk Benefit analysis has not been substantiated adequately based on the results of the presently provided single-course placebo controlled studies (see further). Appropriate multiple-course comparative data versus an optimal established control treatment are lacking.

For the claimed indication, tobramycin has been licensed in EEA. The applicant claims that Cayston could be indicated when tobramycin would not be considered useful, e.g. in case of microbial resistance. However this has not been shown, as yet.

Applicant's retrospective comparison of data from the CP-AI-005 subset of the open uncontrolled follow-up study CP-AI-006 (which showed insufficient consistent results over time) versus matched

control population from the CFF Registry has a very limited value for the assessment of efficacy of Cayston. Furthermore, the degree of matching e.g. with respect to history of treatment for the chronic lung *PA* infection and baseline antibiotic resistant sputum isolates is questionable.

The benefit to public health of the immediate availability on the market of the medicinal product concerned does not outweigh the risk inherent in the fact that additional data are still required.

The applicant will provide the comprehensive clinical data in Q3 2010.

In conclusion, although it is agreed that new medicinal products are warranted for the treatment of chronic airway infections caused by *PA* in CF patients, it has not been shown that aztreonam inhalation would be effective when tobramycin TNS cannot be considered as useful.

Overall, not all criteria needed for granting a Conditional Marketing Authorisation have been met.

Risk-benefit assessment

Benefits

The present short-term efficacy results obtained after a single course of Cayston 75 mg TID are encouraging. However, the durability of the improvements in the treatment-off periods is not sufficiently demonstrated. Furthermore, robust conclusions as to the age dependent performance of Cayston cannot be drawn as subgroups by age were very small, although in all groups there was important treatment difference between AZLI and placebo treated patients. Appropriate evaluation of efficacy and durability of response across different age groups and disease severity in the targeted CF population with the chronic infectious (*PA*) condition requires appropriate controlled trials during at least 3 courses of the inhalational antibiotic. The applicant's proposal during the procedure to limit the indication to *"A 28-day course of Cayston is indicated for the treatment of chronic airway infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 18 years and older to improve pulmonary function and respiratory symptoms. The primary support for this indication is based on two single courses, placebo-controlled studies; a multiple course, comparative, active controlled study is ongoing"*- is not realistic (not practical to be achieved). The claim of the applicant that present data support the "On demand" treatment paradigm cannot be agreed based on present pivotal studies. The applicant acknowledged that the indication remains a chronic indication and as alluded in the reworded posology repetitive courses may be given whenever indicated.

Also, it does not seem realistic to exclude paediatric patients from the indication whereas the targeted disease starts manifesting itself already in children and is still an important serious disease entity in paediatric CF patients. The multiple course results of the Cayston head- to- head comparison with TOBI in the EU study (GS-US-205-0110) remain crucial for the benefit-risk assessment of Cayston in targeted chronic indication.

Risks

There are insufficient long-term safety data after repeated courses with the product (for patients across different age groups) from randomised studies in CF patients with targeted disease. The present safety data are insufficient to resolve the raised safety concerns especially with regard to the risk of acquired resistance, although it is inherent to the use of antibiotics, the concerns are not entirely alleviated. The risk of jeopardising the efficacy of beta-lactam antibiotics for treatment of acute infections in this population remains of concern. A comparative assessment of this issue after multiple treatment courses is of critical importance for the benefit/ risk assessment of Cayston in the sought chronic indication. The results of the ongoing randomised EU Study GS-US-205-0110 are warranted before drawing definitive conclusions with regard to the long-term safety of AZLI.

Finally, the non-clinical concern on the observed C-cell adenoma and its relevance to patients has not been adequately resolved. An important argument of the applicant is the bad prognosis for cystic fibrosis patients who are infected with *Pseudomonas aeruginosa*. However, in children in whom cystic

fibrosis is discovered early and treatment with antibiotics is started early, life expectancy is rising up to 45 years currently. In that situation, the relevance of these tumours is becoming important. Hence, it is still necessary to address the relevance of C-cell adenoma in this specific situation.

Balance

The overall risk-benefit ratio for Cayston is considered unfavourable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Cayston in the treatment of "*chronic airway infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 18 years and older to improve pulmonary function and respiratory symptoms"*was unfavourable and therefore did not recommend the granting of the Conditional Marketing Authorisation of the following reasons:

- There are insufficient long-term efficacy (and durability of response) data after repeated courses with the proposed product (for patients across different age groups) from randomised studies, including active controlled trials.

- There are insufficient long-term safety (and risk of acquired resistance) data after repeated courses with the proposed product (for patients across different age groups) from randomised studies, including active controlled trials.

- The following criteria needed for granting a Conditional Marketing Authorisation have not been met:

    - The Risk Benefit Analysis is unfavourable
    - Fulfilment of unmet medical need has not been substantiated with relevant data;
    - The benefit to public health of the immediate availability on the market of the medicinal product concerned does not outweigh the risk inherent in the fact that additional data are still required.

In addition, the non-clinical concern on the observed C-cell adenoma with its relevance to patients and the two outstanding quality concerns (residual solvent in the active substance and finished product; and impurities in the active substance and finished product) need to be adequately addressed.

2.7 Re-examination of the CHMP opinion of 19 March 2009

Following the CHMP Opinion concluding that the benefit risk of Cayston in the treatment of "*chronic airway infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 18 years and older to improve pulmonary function and respiratory symptoms" was* not considered favourable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant / CHMP position

There are insufficient long-term efficacy (and durability of response) data after repeated courses with the proposed product (for patients across different age groups) from randomised studies, including active controlled trials.

Gilead is seeking conditional approval for a 28-day treatment course of AZLI for adult patients. Currently, approval for a long-term indication is not requested.

The efficacy of AZLI has been evaluated in three Phase 3 studies in 344 unique patients with CF and chronic *PA* infection. In two Phase 3 placebo-controlled studies (CP-AI-007, CP-AI-005), patients

received 75 mg AZLI twice daily (BID; 69 patients) or three times daily (TID; 146 patients) for 28 days. In one open-label follow-on study (CP-AI-006), 274 patients with CF received up to nine 28-day treatment courses of 75 mg AZLI BID or TID. Data presented for the open-label study (CP-AI-006) are from the second interim analysis (12 month).

The AZLI Phase 3 clinical studies employed a number of different efficacy measures. Lung function was assessed with FEV_1 values, respiratory symptoms were assessed with the CFQ-R Respiratory Symptoms scale, and antimicrobial activity was assessed by measuring bacterial density (log_{10} change in *PA* colony forming units [CFUs]). The CFQ-R is the only validated patient-reported outcome (PRO) measure for assessing health-related quality of life in patients with CF. It has been used in numerous clinical intervention and non-intervention studies. The minimal clinically important difference (MCID), the smallest change that a patient recognizes as clinically important, was determined to be a 5-point change on the CFQ-R Respiratory Symptoms scale. The MCID provides a systematic way to interpret changes observed for this efficacy measure. The CFQ-R Respiratory Symptoms scale, which measures clinical symptoms, and FEV_1, which is a physiological measurement of lung function or reversibility of disease, measure related, but non-identical, attributes of CF lung disease. As expected in a heterogeneous population with varying disease severities and treatment histories, these measures showed modest correlations when examined patient-by-patient in the placebo-controlled Phase 3 studies (Retsch-Bogart *et al,* Chest 2009 –in press).

Efficacy of 28-Day AZLI Therapy

Cumulative data from the two placebo-controlled studies (CP-AI-007 and CP-AI-005) and one open-label follow-on study (CP-AI-006) provide substantial evidence of the effectiveness of a 28-day treatment course of 75 mg AZLI TID in diminishing respiratory symptoms and improving pulmonary function in patients with CF. The magnitude of the changes in FEV_1 and CFQ-R Respiratory Symptoms scores were consistent among AZLI-treated patients in all three studies, and superior to placebo in both pivotal studies (Figures 1&2).

Figure 1. Mean Relative Change in FEV_1 % Predicted Following 28-Day AZLI Treatment Courses

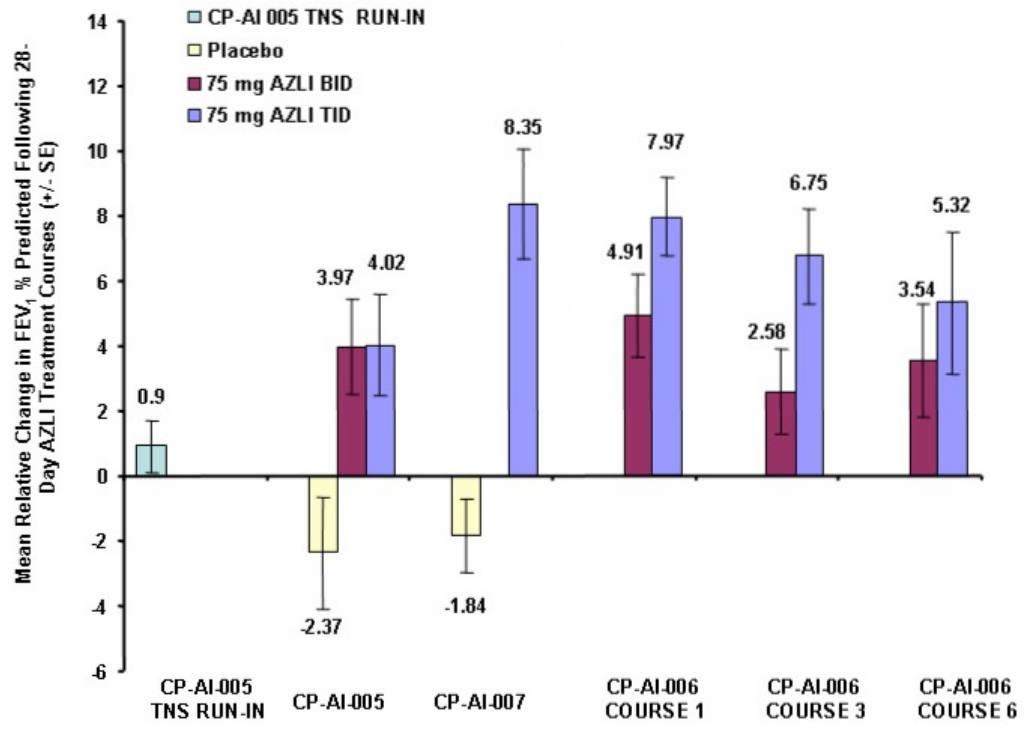
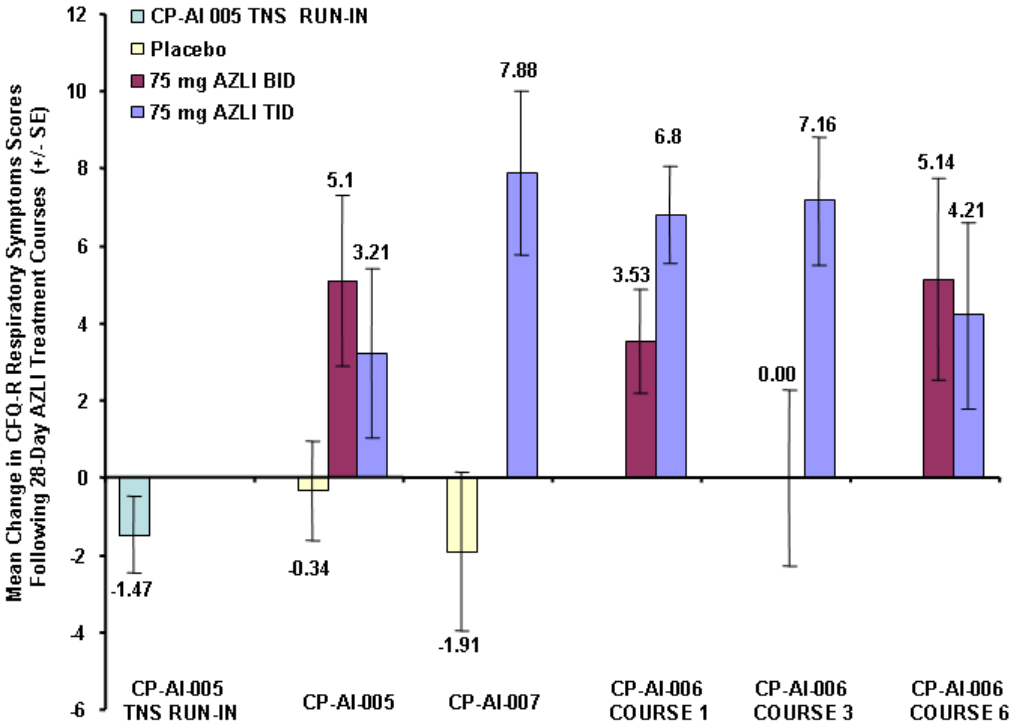


Figure 2. Mean Change in CFQ-R Respiratory Symptoms Scores Following 28-Day AZLI Treatment Courses



Study CP-AI-005 included a 28-day open-label TNS lead-in period prior to the 28-day double-blind AZLI/placebo treatment period. Mean efficacy responses to TNS were poor during this lead-in period; mean CFQ-R Respiratory Symptoms scores decreased (worsened) by 1.47 points, mean FEV_1 increased by 0.9%, and mean sputum *PA* density decreased by 0.28 $\log_{10}$ *PA* CFU/g sputum. In contrast, AZLI treatment improved lung function in TNS-experienced patients, including those who were non-responsive to TNS therapy. The magnitude of the improvements in FEV_1 and CFQ-R Respiratory Symptoms scores were much larger after 28-days of AZLI treatment than after the 28-day TNS run-in treatment, in spite of the fact that the AZLI treatment period immediately followed the TNS treatment period. These data clearly demonstrate that AZLI is effective among TNS-experienced patients, including patients with attenuated responses to TNS therapy.

AZLI-treated patients demonstrated improvements in clinical outcome measures, regardless of baseline disease severity, age, or the presence or absence of antibiotic-resistant *PA* at baseline. In the placebo-controlled studies, the difference between patient responses to administration of study drug or placebo for 28-days, i.e., treatment effect, constituted the primary endpoint. The treatment effect in study CP-AI-007 for percent change in FEV_1 among patients in the more severe disease category ($FEV_1 \leq 50\%$ of predicted) was nearly identical to that for patients in the less severe disease category ($FEV_1 > 50\%$ of predicted) (Table 1). Similar analyses from study CP-AI-005 also demonstrated AZLI efficacy across subgroups defined by baseline disease severity.

Table 1. Percent Change in FEV_1 (L) at Day 28 from Day 0 by Baseline Disease Severity: CP-AI-007

Baseline Disease Severity	Treatment	
	Placebo (N = 84)	75 mg AZLI (N = 80)
FEV_1 % of predicted ≤ 50%		
N	30	30
Mean (± SD)	-4.031 (11.933)	6.343 (15.997)
Adjusted mean	-4.002	6.314
Treatment difference: 75 mg AZLI – placebo	10.316	
95% CI (p-value)	3.066, 17.566 (0.0061)	
FEV_1 % of predicted > 50%		
N	54	50
Mean (± SD)	-0.632 (9.401)	9.564 (14.779)
Adjusted mean	-0.602	9.531
Treatment difference: 75 mg AZLI – placebo	10.133	
95% CI (p-value)	5.320, 14.945 (< 0.0001)	

Source: CP-AI-007 CSR Adhoc Table 5

The treatment effects in study CP-AI-007 for percent change in FEV_1 (L) were comparable for children (6 to 12 years), adolescents (13 to 17 years), and adults (≥ 18 years) (Table 2). Similar analyses from study CP-AI-005 also demonstrated AZLI efficacy across subgroups defined by age.

Table 2. Percent Change in FEV_1 (L) at Day 28 from Day 0 by Age Group: CP-AI-007

Age Group	Treatment	
	Placebo (N = 84)	75 mg AZLI (N = 80)
Children (6-12 years)		
N	4	11
Mean (± SD)	1.837 (20.950)	7.100 (23.327)
Adjusted mean	-8.245	2.985
Treatment difference: 75 mg AZLI – placebo	11.230	
95% CI (p-value)	-20.224, 42.684 (0.4486)	
Adolescents (13-17 years)		
N	12	10
Mean (± SD)	-3.442 (11.234)	9.331 (13.382)
Adjusted mean	-5.422	8.493
Treatment difference: 75 mg AZLI – placebo	13.915	
95% CI (p-value)	3.388, 24.443 (0.0124)	
Adults (≥ 18 years)		
N	68	59
Mean (± SD)	-1.781 (9.655)	8.425 (13.920)
Adjusted mean	-2.412	8.136
Treatment difference: 75 mg AZLI – placebo	10.548	
95% CI (p-value)	6.365, 14.730 (< 0.0001)	

Source: CP-AI-007 CSR Table 14.2.18.1

The potential for developing antibiotic resistance is an important concern associated with repeated administration of any antibiotic therapy. Presumably the clinical efficacy of the antibiotic declines as antibiotic resistance develops. Furthermore, acquisition of a particular antibiotic resistance mechanism by a bacterial population may also result in cross-resistance to other antibiotics, both within and across classes of antibiotics. Therefore, the development of antibiotic resistance could limit the antibiotic treatment options available to patients with CF during a pulmonary exacerbation.

In the Phase 3 placebo-controlled and open-label follow-on studies, no trends toward increased *PA* resistance to aztreonam or other antibiotics commonly used to treat CF exacerbations were observed following single or repeated 28-day courses of AZLI therapy. Two key factors are likely contributing to this lack of development of resistance: the mechanism of action of aztreonam and the delivery of high concentrations of aztreonam directly to sites of infection via inhalation administration.

Additional analyses were conducted to evaluate whether the presence of antibiotic-resistant *PA* at study baseline could preclude a patient from demonstrating a positive clinical response to AZLI therapy. In Study CP-AI-007, improvements in respiratory symptoms and pulmonary function, and reductions in sputum *PA* density, were observed for AZLI-treated patients with or without *PA* isolates that were multi-drug resistant and with or without *PA* isolates that were beta-lactam resistant at baseline (Table 3). Thus, AZLI provided clinical benefit to patients regardless of whether or not antibiotic-resistant *PA* was present at baseline.

Table 3. Clinical Efficacy Outcomes at Day 28 for Patients with Antibiotic-Resistant *PA* at Baseline: CP-AI-007

	Change in CFQ-R Respiratory Symptoms Score at Day 28			**Percent Change in FEV_1 (L) at Day 28**			**Change in log_{10} *PA* CFU Density in Sputum at Day 28**		
	Mean	SD	N	Mean	SD	n	Mean	SD	n
Placebo (N = 84)									
Resistance to All 5 Beta-Lactams	-7.94	13.93	7	-3.72	6.91	7	-0.40	0.29	4
Resistance to < 5 Beta-Lactams	-0.20	18.94	68	-1.90	11.08	69	-0.03	0.80	53
Multidrug-resistant* *PA*	-0.65	19.60	43	-3.05	10.81	43	-0.12	-0.62	31
No Multidrug-resistant *PA*	-1.30	17.44	32	-0.80	10.69	33	0.02	0.94	26
AZLI TID (N = 80)									
Resistance to All 5 Beta-Lactams	3.97	20.49	14	7.05	13.83	14	-0.49	0.74	10
Resistance to < 5 Beta-Lactams	9.04	19.83	55	9.46	16.23	55	-2.01	2.56	40
Multidrug-resistant *PA*	6.67	16.79	45	9.51	14.76	45	-1.35	2.38	32
No Multidrug-resistant *PA*	10.53	24.98	24	7.95	17.65	24	-2.34	2.31	18

Source: EMEA Table 67.3.1

* Multidrug resistance is defined as having resistance to at least one of the antibiotics in two of the three drug classes (aminoglycosides, beta-lactams, quinolones).

Durability of AZLI Response

The AZLI treatment effect was durable over multiple courses and the efficacy responses were larger with TID than with BID administration. The primary objective of the open-label follow-on study, CP-AI-006, was to assess safety; a secondary objective was to determine the effects of repeated courses of AZLI therapy on disease-related endpoints, including lung function and respiratory symptoms. Data from study CP-AI-006 were used to determine the durability of the AZLI treatment effect and the optimum dosing regimen (BID vs TID) in a patient population that reflected a realistic spectrum of CF disease severity and treatment histories. In the second interim analysis (12 month) of Study CP-AI-006, FEV_1 % predicted (Figure 3) and CFQ-Respiratory Symptoms scores (Figure 4) showed consistently positive results across multiple courses of AZLI TID. Data from this interim analysis also provided evidence of a dose response; treatment responses were consistently larger for the TID group than for the BID group.

Figure 3. Mean Relative Change in FEV_1 % Predicted from Baseline

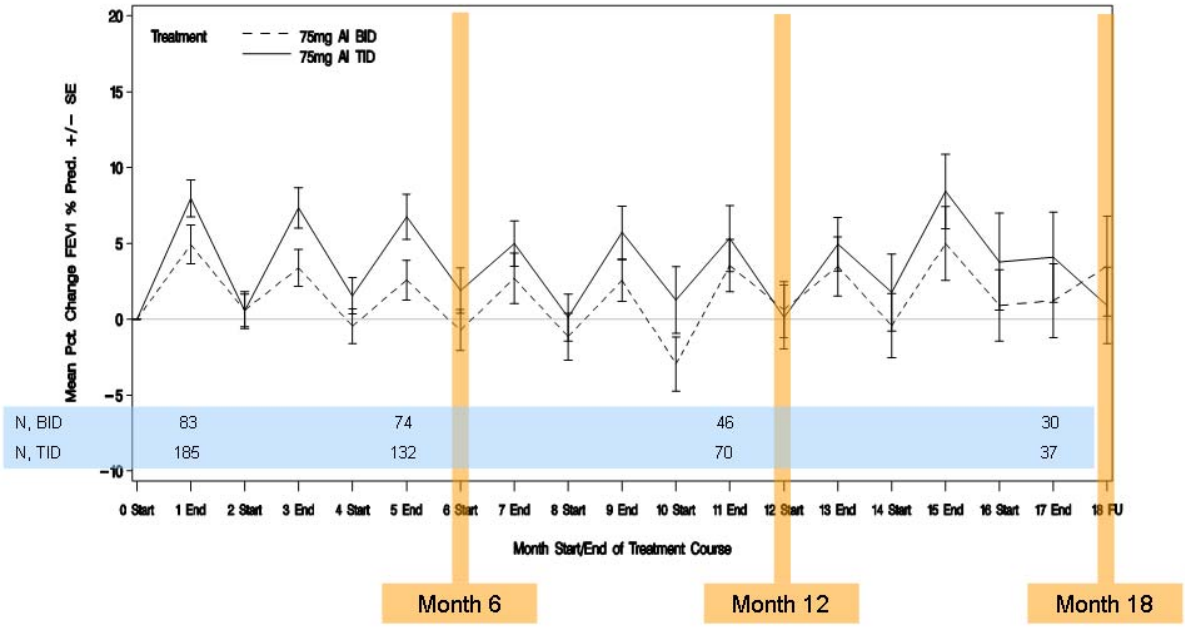
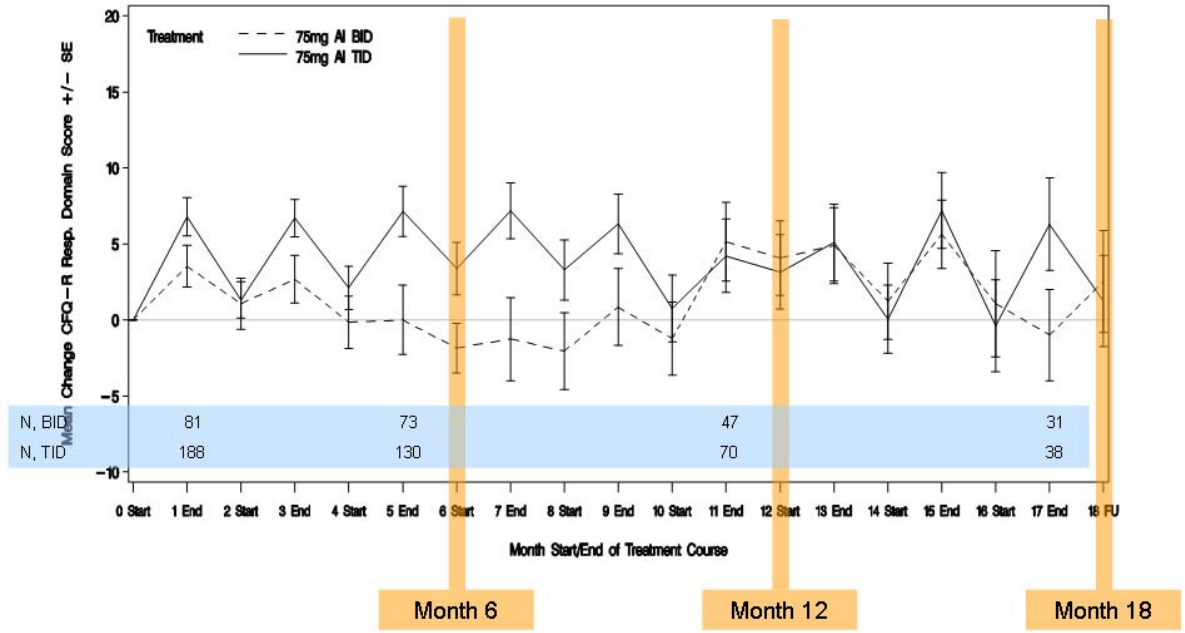


Figure 4. Mean Change in CFQ-R Respiratory Symptoms Scores from Baseline



Comparison of AZLI and Historical TNS Efficacy

The AZLI treatment effect appeared comparable or better in magnitude and duration than the TNS treatment effect observed for adults in the TNS pivotal registration trials conducted more than a decade ago. In adults, the FEV_1 effect following treatment with TNS was about 5% at 6 months and a loss in lung function was observed during the 18-month open-label follow-on study, when compared with baseline values. Gilead is requesting an indication for CF patients aged 18 years and older; therefore, the adult cohort of the TNS registration trial is the appropriate comparator group. In Study CP-AI-007, AZLI significantly improved lung function in patients with CF. Seventy-seven percent of the patients in Study CP-AI-007 were adults (≥ 18 years) and the treatment effect for percent change in FEV_1 was 10.5% for the adult patient subset. This treatment effect appears to be comparable or larger than that observed for TNS-treated adults in the TNS registration trials.

The durability of the FEV_1 treatment effect following administration of AZLI also appeared comparable or better than that observed in the pivotal TNS registration trials. The majority of patients (80%) enrolled in the open-label follow-on study (CP-AI-006) were adults. Patients in this study experienced consistent improvements in lung function over multiple courses of AZLI therapy, includes data from all patients in the study at the second interim analysis [12 months]). This contrasts with the decline in lung function observed among adults during repeated courses of TNS therapy in the TNS registration studies.

It is difficult to draw conclusions from comparisons of clinical trial data from different studies, conducted nearly a decade apart in time; nonetheless, the AZLI treatment effect in adults for FEV_1 appears comparable or better in magnitude and duration than that observed for TNS in the pivotal registration trials.

Conclusion

Data from the Phase 3 AZLI studies demonstrated the clinical efficacy of a 28-day treatment course of 75 mg AZLI TID in decreasing respiratory symptoms and improving pulmonary function in patients with CF. Clinical improvements were observed among AZLI-treated patients, regardless of age, disease severity, and presence or absence of antibiotic-resistant *PA* at baseline. The results of study CP-AI-006 further provided some support to the durability of response to AZLI therapy, as improvements in lung function and respiratory symptoms following AZLI therapy were maintained above baseline values for 18 months in this predominantly adult population. The magnitude of the improvements in lung function and respiratory symptoms scores were consistent among AZLI-treated patients in all three studies, and superior to placebo-treated patients in both pivotal studies. Furthermore, although it is difficult to draw conclusions from comparisons of clinical trial data from different studies, conducted nearly a decade apart in time, the AZLI treatment effect in adults for FEV_1 appears comparable or better in magnitude and duration than that observed for TNS in the pivotal registration trials.

CHMP position

The CHMP can agree that adults represent a significant proportion of the total CF patient population and the vast majority of chronically PA-infected patients.

In the studies presented, AZLI had an undisputable effect on lung function. Decline in FEV1 represents airflow limitation due to chronic airway disease, airway remodelling and related changes in elastic recoil. In the studies CP-AI-005 AZLI, BID and TID and in the study CP-AI-007 AZLI TID (in which 77% were adults), significant increases were observed in FEV1, after a 28 day treatment course with AZLI. For both studies, the effects are significant compared to placebo. The effects in the CPAI-005 study, although somewhat more modest, are even more remarkable since the effect is obtained immediately after a 28-day treatment with inhaled tobramycin. In comparison, the direct effects of inhaled tobramycin were, in terms of FEV1 improvement, very modest (0.9% increase).

It is also encouraging to note that the treatment effect on lung function and respiratory symptoms seems to persist over various treatment courses. However this has to be interpreted with the caveat that these data were obtained in uncontrolled circumstances and with possible resort to concomitant drugs against *Pseudomonas aeruginosa* (at the investigator's discretion). Hence, the applicant tends to compensate for these limitations by making an historical comparison with data derived from the tobramycin registration trials. However, as rightly pointed by the applicant one should beware of drawing conclusion "from comparisons of clinical trial data from different studies, conducted nearly a decade apart in time". Only a head-to-head comparison could have been regarded as a valid demonstration to this purpose. These confirmatory data are awaited.

There are insufficient long-term safety (and risk of acquired resistance) data after repeated courses with the proposed product (for patients across different age groups) from randomised studies, including active controlled trials.

Safety Profile

Overall, the observed adverse event (AE) profile in the two US Phase 3 placebo-controlled studies, CP-AI-005 and CP-AI-007, was consistent with the signs and symptoms of CF lung disease and the incidence of most AEs was similar to that of placebo. The few adverse reactions (ARs) attributable to AZLI were primarily self-limiting, local effects associated with inhalation of the medication; there were no serious allergic reactions and few serious adverse events (SAEs) associated with AZLI. The majority of events reported as SAEs were associated with hospitalization for symptoms of pulmonary exacerbations.

Analysis of the safety results from the two placebo-controlled studies identified eight AEs as potentially causally related to AZLI: chest discomfort, cough, nasal congestion, pharyngolaryngeal pain, pyrexia, rash, rhinorrhoea, and wheezing. These eight AEs were therefore designated as ARs. It is difficult to interpret a comparison of ARs in the 28-day placebo-controlled Phase 3 studies and the second interim analysis (12 months) of the open-label study because the studies were of different lengths. Therefore the ARs were adjusted for study duration and are presented as rates (number of events per patient-month). For the eight ARs, the rates observed during Study CP-AI-006 were no higher than those observed for patients in the pooled AZLI group of the integrated US Phase 3 placebo-controlled studies (Table 4), indicating that they do not increase with longer exposure to AZLI.

Table 4. Adverse Reactions[a] (AEs) Adjusted for Study Duration: Comparison of Study CP-AI-006 with Integrated US Phase 3 Placebo-controlled Studies

Preferred Term	***Number of Occurrences per Patient-month[b]***		
	Integrated US Phase 3 Placebo-controlled Studies		***Study CP-AI-006 [c]***
	Placebo (N = 160) (275 Pt-months)	***Pooled AZLI[d] (N = 215) (442 Pt-months)***	***Pooled AZLI (N = 274) (3001 Pt-months)***
Chest discomfort	0.040	0.059	0.038
Cough	0.356	0.387	0.275
Nasal congestion	0.073	0.097	0.046
Pharyngolaryngeal pain	0.062	0.068	0.057
Pyrexia	0.036	0.088	0.053
Rash	0.011	0.009	0.007
Rhinorrhoea	0.040	0.041	0.038
Wheezing	0.065	0.072	0.030

Source: US NDA 120-Day Safety Update (Module 5, Section 5.3.5.3) Tables 14.2.5.1 and 14.2.5.4. – available on request.

[a] Adverse reactions are events that were considered to be reasonably associated with the use of AZLI in the US Phase 3 placebo-controlled trials.

[b] Rates are the number of occurrences per patient-month. Patient-months are calculated by summing study duration (days) for all patients and dividing by 28.

[c] Data are from the second interim analysis of Study CP-AI-006.

[d] The pooled AZLI group includes TID patients from CP-AI-005 and -007 as well as AZLI BID patients from CP-AI-005.

Six of the eight ARs were reported as SAEs at rates of ≤ 0.002 events per patient-month in Study CP-AI-006. SAEs of cough were observed at a higher rate in CP-AI-006 than in the integrated US Phase 3 placebo-controlled trials, and the rate of pyrexia SAEs in Study CP-AI-006 was comparable to that of AZLI-treated patients and lower than placebo patients in the integrated US Phase 3 placebo-controlled trials.

Bronchospasm (defined in the AZLI studies as ≥ 15% decline in FEV_1 following dosing) is a potential complication associated with any inhaled medication. There were slight decreases in mean FEV_1 30 minutes after AZLI treatment in the Phase 3 studies, but few patients experienced bronchospasm at

any clinic visit. Evaluation of airway reactivity by treatment interval provided no evidence that bronchospasm worsens with repeated exposure to AZLI.

In the Phase 3 placebo-controlled studies, there were no statistically significant differences in SAEs observed between the pooled placebo and pooled AZLI groups. Overall, the rates of SAEs that were reported in Study CP-AI-006 but not in AZLI-treated patients in the integrated US Phase 3 placebo-controlled studies were low (≤ 0.004 events per patient-month in CP-AI-006, with the exception of exercise tolerance decreased [0.007 events per patient-month in both CP-AI-006 and placebo patients]). Given the low rates of these SAEs and the difference in length of study participation, these observations do not suggest any safety concerns.

There were no deaths reported in the CP-AI-007 or CP-AI-005 placebo-controlled studies. Two deaths were reported in Study CP-AI-006. One patient died following completion of eight courses of AZLI. Another patient died approximately 1.5 months after withdrawing from the study, following completion of three courses of AZLI. For both of these patients, the investigator did not believe the death to be related to AZLI treatment.

In addition to the positive safety profile demonstrated in clinical trials to date with AZLI, the safety of the parenteral formulation of aztreonam (Azactam®) has been established with over 20 years of extensive clinical use in the EU and US for the treatment of serious gram-negative infections. Azactam has been generally well tolerated, locally and systemically, by various patient groups, including those with CF. Systemic exposure to aztreonam following inhalation of AZLI is much lower than that following IV or IM administration of Azactam. Therefore, no new safety issues are expected to be seen with the inhaled formulation of aztreonam (AZLI).

Risk of Acquired Resistance

The risk of acquired resistance is inherent to the use of all antibiotics, particularly in the management of CF patients with chronic *PA* infection, in which eradication generally cannot be achieved. The development of antibiotic resistance is assessed by measuring changes over time in the minimum concentrations of an antibiotic that inhibit 50% and 90% (MIC_{50} and MIC_{90}, respectively) of *PA* isolates.In the Phase 3 placebo-controlled studies, changes in *PA* susceptibility to aztreonam were not observed following a single 28-day course of 75 mg AZLI (Table 5).

Table 5. MIC_{50} and MIC_{90} of Aztreonam (µg/mL) for the *PA* Isolate with the Highest MIC from Each Patient: Integrated US Phase 3 Placebo-controlled Studies

	Result (µg/mL)		
	MIC_{50}*	MIC_{90}*	n
Pooled Placebo (N = 160)			
Day 0	8	128	147
Day 14	4	128	146
Day 28	4	128	132
Day 42	4	64	113
Pooled AZLI (N = 215)			
Day 0	4	128	191
Day 14	8	128	195
Day 28	8	256	174
Day 42	8	128	173

Source: SCM Table 3.6.1.4.
n = number of patients with available data.
* ± 2-fold change in MIC is considered *unchanged*.

The overall susceptibility of *PA* to aztreonam also remained unchanged during treatment with repeated 28-day courses of 75 mg AZLI TID in the open-label follow-on study (Table 6). Further, no cross-resistance to other antibiotics, including aminoglycosides, quinolones, and beta-lactams, has been observed following up to six 28-day courses of 75 mg AZLI TID.

Table 6. MIC_{50} and MIC_{90} of Aztreonam (µg/mL) for the *PA* Isolate with the Highest MIC from Each Patient: CP-AI-006

	Result (µg/mL)		
	MIC_{50} *	MIC_{90} *	n
AZLI TID (N = 189)			
Baseline	8	256	172
End AZLI Course 1	8	256	172
End AZLI Course 2	8	512	147
End AZLI Course 3	16	512	112
End AZLI Course 4	16	512	82
End AZLI Course 5	16	512	76
End AZLI Course 6	16	512	65

Source: 120-Day Safety Report Table 14.7.5.
Data from the second interim analysis of CP-AI-006 (12 months).
n = number of patients with available data.
* ± 2-fold change in MIC is considered *unchanged*.

Conclusion

The Phase 3 AZLI studies, which demonstrate that AZLI is safe and does not induce acquired resistance, and are sufficient to support the proposed 28-day indication. Overall, the AE profile observed during these studies was dominated by respiratory events, consistent with the expected signs and symptoms of underlying CF disease. The incidences of these AEs were comparable between AZLI and placebo treatment groups, with the exception of pyrexia (fever), which occurred with higher incidence among AZLI-treated patients. Further, in the 18-month open-label follow-on study, no new safety signals were identified, no increased rate of AEs over multiple AZLI treatment courses was detected, and no development of antibiotic resistance was observed. These data, combined with over 20 years of intravenous aztreonam use, support the long-term safety profile of AZLI therapy.

CHMP position

For the 28 days course no obvious differences were seen between placebo and active groups. More relevant however is the pooled analysis in study CP-AI-006. In that analysis there was no increase in the AE when compared to the single 28 day course. Also wheezing, which could indicate bronchial hyper-responsiveness due to the inhalation was not increased over time. These data, also over the longer time period in study 006, are reassuring.

Concerning resistance, the applicant states that based on the data derived from the integrated US phase III placebo controlled studies, changes in PA susceptibility to aztreonam were not observed following a single 28-day course of 75 mg AZLI. No cross resistance to other antibiotics, including aminoglycosides, quinolones, and beta-lactams, has been observed following up to six 28-day courses of aztreonam. Although reassuring at first, it is noted that consulted experts (SAG-AI) remarked that standard microbiological sensitivity testing techniques may lack sensitivity to pick up mixed resistant and susceptible bacterial populations in the sputum, and establish the number of susceptible relative to resistant isolates from individual patients. In that sense, and because many isolates are resistant at start of therapy, it is difficult to interpret the resistance data for trial CP-AI-006. Notwithstanding the

posed limitations, long-term resistance data may eventually answer the question, best if obtained in a head-to head comparison trial.

The following criteria needed for granting a Conditional Marketing Authorisation have not been met:

- ***The Risk Benefit Analysis is unfavourable***

Gilead believes that 75 mg AZLI TID has a positive risk-benefit assessment for the requested 28-day therapeutic indication in adults.

In the two Phase 3 placebo-controlled studies, AE rates were comparable between the AZLI and placebo treatment groups, with the exception of pyrexia (fever), which was statistically higher in the AZLI group. A 28-day AZLI treatment course was not associated with acquired resistance to aztreonam or the selection of *PA* isolates that were highly resistant to aztreonam. Further, there was no association between a 28-day course of AZLI and acquired *PA* resistance to any other antibiotic tested. Statistically and clinically significant improvements in multiple disease-related endpoints were observed for AZLI-treated patients compared with placebo-treated patients, including pulmonary function, time to need for other anti-pseudomonal antibiotics, respiratory symptoms, and sputum *PA* density. These clinical responses were equal to or greater in magnitude than previously tested therapies for CF lung disease in an adult population. Further, the 18-month open-label follow-on study showed maintenance of treatment effects over multiple cycles of AZLI therapy, no new safety signals, no increased rate of AEs, and no development of antibiotic resistance. Therefore, there is little risk that a new safety signal will appear in the ongoing 6-month comparative study. In addition, over 20 years of intravenous aztreonam use has led to a large safety database that provides additional reassurance that the risk of detecting a novel idiosyncratic event is minimal.

The risk of selecting for drug-resistant pathogens is inherent to the use of all antibiotics. This risk is perhaps greater in patients with CF because complete clearance of respiratory pathogens is generally not achieved. The primary risk associated with acquired resistance is the loss of intravenous aztreonam or other beta-lactam antibiotics for the treatment of respiratory exacerbations. Recurrent shortages of intravenous aztreonam in Europe have limited the use of aztreonam in patients with CF. Examination of practice patterns in the US suggests that intravenous aztreonam was administered to 2.1% of patients with exacerbations of respiratory infections; thus, this therapeutic option is used only infrequently to manage acute pulmonary exacerbations.

Placebo-controlled studies of single 28-day courses of AZLI along with one open-label study of multiple courses of AZLI have demonstrated a strong safety and efficacy profile without development of antibiotic resistance.

For the reasons given above, the applicant believes that the overall risk-benefit evaluation of a 28-day course of AZLI therapy is favourable.

- ***Fulfilment of unmet medical need has not been substantiated with relevant data;***

Chronic *PA* airway infection is incurable and currently available therapies do not prevent disease progression. Although CF is a chronic disease, short courses of intravenous and oral antibiotics are commonly used to treat exacerbations or improve symptoms as part of standard of care. This on-demand treatment paradigm allows for assessment of individual patient responses to therapy; however, current outpatient treatment options are limited primarily to intravenous aminoglycosides and beta-lactams in 2-4 week treatments and oral ciprofloxacin in 2-3 week treatments. Physicians currently prescribe repeated courses of these approved on-demand therapies according to patient needs as standard of care. Administration of the proposed 28-day course of AZLI to improve lung function and respiratory symptoms is consistent with the on-demand treatment paradigm.

The European Respiratory Society (ERS) states that "pulmonary disease is a major cause of mortality and morbidity in CF; hence, innovative treatments need to be aimed primarily at the airways". In addition, the ERS notes that "new antimicrobial agents are needed to combat infections, particularly for organisms which are increasingly resistant to the currently available drugs.".

AZLI is a new inhaled formulation of the parenteral antibiotic aztreonam and provides several advantages over current inhaled antibiotics, namely aminoglycosides such as TNS. The mechanism of action of aztreonam is different from that of aminoglycoside antibiotics and thus use of AZLI should not contribute to the emergence of aminoglycoside-resistant strains of *PA*. Further, aztreonam has demonstrated activity against aminoglycoside- and multi-drug resistant *PA*, as well as several other CF pathogens with intrinsic resistance to aminoglycosides, including *Burkholderia spp*. Finally, aztreonam does not cause ototoxicity or nephrotoxicity, which are side effects associated with aminoglycosides.

The predominant unmet medical need is for new antipseudomonal antibiotic therapies in the adult population, as the vast majority of CF patients with severe lung disease and multi-drug resistant *PA* are adults. TNS has been on the market in Europe and the US for nearly a decade. In 2006, approximately 62% of patients with CF in the US received TNS, and about 40% used it chronically. Independent research has shown similar or lower use in the EU (Gilead, data on file). The majority of CF patients with chronic *PA* infection are now older than 18 years; in the Phase 3 AZLI studies conducted in 2005-2008, 80% of patients were older than 18 years. In comparison, approximately 50% of the patients were older than 18 years in the TNS registration trials conducted in 1995-1996, and the large improvements in lung function were primarily due to the large responses in children and adolescents. In the TNS registration trials, the FEV_1 effect in adults was approximately 5% at 6 months and decreased from baseline values during the 18-month open-label extension study. Publication of the pooled data for all age groups from the controlled trial and selective publication of the 18-month open-label extension data have led to a mistaken impression that the effects of TNS in adults are large and persistent. The observation that the FEV_1 benefit in adults appeared to be smaller than the benefit in adolescents or children raises questions about the current efficacy of TNS in a disease population that is becoming predominantly adult. After a decade of use, TNS has an attenuated effect and the FEV_1 benefit in adults has always been less than the benefit in adolescents.

Several studies conducted during the past decade have evaluated the microbiologic response (change in $\log_{10}$ *PA* CFU density) to TNS therapy. Reductions in sputum *PA* CFU density during TNS therapy have diminished over the past decade, likely due in part to increased *PA* resistance to tobramycin resulting from widespread chronic use of TNS. The mean reduction in sputum *PA* density following 28-day TNS therapy in Study CP-AI-005 was 0.28 $\log_{10}$ CFU. This treatment effect contrasts sharply with the 0.86 $\log_{10}$ CFU reduction observed by Hodson et al. in a European trial and the approximately 2 $\log_{10}$ CFU reductions observed following one 28-day TNS course in the registration trials. The current product label for TNS reports that "reductions in sputum bacterial density were smaller in each successive trial," acknowledging the diminishing microbiologic efficacy of this drug. The addition of another anti-pseudomonal antibiotic for inhalation, such as AZLI, would fill an important void.

In the decade of TNS use following completion of these studies, there have been no long-term follow-up studies of TNS clinical efficacy. Tobramycin resistance in *PA* isolates from demographically similar CF patients has increased from 5.4% in the TNS trials in 1998 to 20.0% in 2008. Following the 28-day lead-in TNS period in study CP-AI-005, the mean FEV_1 effect was less than 1%. Further analyses showed a clear breakpoint for clinical response to TNS at the parenteral susceptibility breakpoint (4 μg/mL) (Table 7).

Table 7. Relationship between Clinical Efficacy of TNS Therapy and *PA* Resistance to Tobramycin: CP-AI-005

Least Susceptible PA Isolate at Baseline	***N****	***Clinical Efficacy Outcomes Following 28-day Therapy 300 mg TNS BID***		
		Change in CFQ-R Respiratory Symptoms Score Mean (SD)	***Percent Change in FEV_1 [L] Mean (SD)***	***Change in Log_{10} PA CFU Density in Sputum Mean (SD)***
Tobramycin Susceptible (MIC ≤ 4 μg/mL)	113	0.15 (13.92)	2.39 (11.47)	-0.74 (1.61)
Tobramycin Resistant (MIC > 4 μg/mL)	73	-2.89 (14.96)	-1.12 (11.65)	0.11 (1.40)

N* = number of patients with available data for at least 1 of 3 efficacy endpoints.

Patients with tobramycin-resistant *PA* (MIC > 4 μg/mL) demonstrated no mean improvements in respiratory symptoms, pulmonary function (FEV_1), or sputum *PA* CFU density following the 28-day lead-in course of TNS. Furthermore, TNS-treated patients with tobramycin-susceptible *PA* isolates (MIC ≤ 4 μg/mL) demonstrated minimal changes in respiratory symptoms and pulmonary function despite a measurable reduction in sputum *PA* CFU density. This is in contrast to AZLI-treated patients with *PA* isolates resistant to a variety of drug classes, who showed improvement in each of these clinical outcome measures.

Conclusion

In summary, there is an unmet medical need for additional and alternate treatment options for adults with chronic *PA* infection, severe lung disease, and multi-drug resistant *PA*. AZLI provides several advantages over current inhaled antibiotics, due to its mechanism of action, safety profile, and demonstrated clinical efficacy in patients with antibiotic-resistant *PA*.

- ***The benefit to public health of the immediate availability on the market of the medicinal product concerned does not outweigh the risk inherent in the fact that additional data are still required.***

Many adult patients with CF have severely compromised lung function subsequent to numerous years of airway infection with *PA*. These patients often have little or no response to most available outpatient therapies and their current treatment options include long-term inpatient or outpatient intravenous antibiotics. AZLI could be made immediately available to these patients, and would be a superior option to current therapies for several reasons: 1) the high airway concentration of aztreonam following inhalation of AZLI allows effective treatment of multi-drug resistant *PA* infections that are likely to be poorly responsive or non-responsive to intravenous therapies; 2) inhaled antibiotics, such as AZLI, have a lower systemic exposure than intravenous antibiotics, such as aztreonam, and AZLI has a proven safety profile when administered for a 28-day course; 3) indwelling chronic venous access catheters would not be needed in patients treated with an inhaled antibiotic; and 4) the two to three minute AZLI TID treatment time would be dramatically more convenient, when compared with treatment times for intravenous antibiotics.

AZLI's greatest utility is in older patients; since the incidence of chronic *PA* airway infection in patients with CF increases with age, there remains a particular unmet medical need for viable treatment options in adults. The Rapporteur expressed concern about potential off-label use of AZLI in paediatric patients; however, there is less immediate need for AZLI in this population as there are other approved effective therapies for younger patients. With improved care with CF, including the potential for eradication therapy of initial *PA* infection, fewer paediatric patients have all the following: chronic *PA* airway infection, severely compromised lung function, and failure to respond to currently available agents.

Conditional approval would not impact Gilead's ability to fully enroll and complete all ongoing studies.

Conclusion

The applicant believes there are sufficient data to support the benefit to public health of the immediate availability of AZLI as a treatment option for adult CF patients with chronic *PA* airway infection, and the additional data requested for full evaluation of AZLI will be available within the next 14 months.

CHMP position

The MAH considers that there is an unmet medical need for additional and alternate treatment options for adults (and children) with chronic *PA* infection, severe lung disease, and multi-drug resistant *PA*. The CHMP accepts that the AZLI therapy might fulfil such a need by demonstration of short term efficacy without significant adverse events or development of resistance, being sufficient in the framework of a conditional Marketing Authorisation. Additional data on sustainability of the observed short term benefit, resistance potential and adverse events remain outstanding.

In addition, CHMP accepts that based on the limited data provided to date (primarily based on the two single 28 day course placebo-controlled trials), the benefit-risk profile is considered positive, for an indication stated "as suppressive treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis".

Also, CHMP agrees with the applicant that for the stated patient population, the data support the benefit to public health of the immediate availability of AZLI as a treatment option for adult CF patients with chronic *PA* pulmonary infection and outweigh the risk inherent in the fact that additional data are still required.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group. The CHMP concluded that in relation to:

Ground of refusal # 1, the data to support the sustainability of the observed short term efficacy over subsequent courses of treatment are limited.

Ground of refusal # 2, the data to support the sustainability of the observed short term safety (and risk of acquired resistance) over subsequent courses of treatment are limited.

Ground of refusal #3, based on the limited data provided to date (primarily the two single 28 day course placebo-controlled trials), (1) the benefit-risk profile is considered positive, for short term suppressive treatment of chronic pulmonary infections due to *Pseudomonas aeruginosa* in adult patients with cystic fibrosis; In this patient population, (2) Cayston fulfils an unmet medical need and (3) the data support the benefit to public health of the immediate availability of Cayston as a treatment option, outweighing the risk inherent in the fact that additional data are still required.

2.8 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan:

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risks		
Bronchospasm	Regular analysis of postmarketing safety data Review of pulmonary function data in the clinical study GS-US-205-0110	**Proposed SmPC text:** **Section 4.4** *Bronchospasm* Bronchospasm is a complication associated with nebulised therapies. 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
Important Potential Risks		
Serious hypersensitivity reactions (including erythema multiforme, exfoliative dermatitis, urticaria, rash, petechiae, pruritis, purpura, and pyrexia [with diaphoresis]). See also anaphylaxis and toxic epidermal necrolysis below	Regular analysis of postmarketing safety data Review of adverse event data in the following clinical studies GS-US-205-0110 and GS-US-205-0117.	**Proposed SmPC 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 drug 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, pruritis, diaphoresis. **Section 4.8** *Skin and subcutaneous tissue disorders* Common: rash The following rare and severe adverse drug 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, pruritis, diaphoresis.
Anaphylaxis	Routine pharmacovigilance	**Proposed SmPC text:** See above for Serious Hypersensitivity Reactions.
Toxic epidermal necrolysis	Routine pharmacovigilance	**Proposed SmPC text:** See above for Serious Hypersensitivity Reactions.
Colonization leading to superinfection	Regular analysis of postmarketing safety data Review of microbiology data, data on medications prescribed and monitoring of AEs (including pneumonia, meningitis, bacteremia, sinusitis, cellulitis, and otitis media) indicating fungal or bacterial superinfections and adverse event data in the following clinical studies: CP-AI-006, GS-US-205-0110 and GS-US-205-0117	**Proposed SmPC 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	Regular analysis of postmarketing safety data Review of susceptibility data in the following clinical studies:	**Proposed SmPC text:** **Section 4.4** The development of antibiotic-resistant

	CP-AI-006, GS-US-205-0110 and GS-US-205-0117	*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** 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 hydrolyze 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 hydrolyze 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 hydrolyze 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 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 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 pediatric and adolescent patients (under 18 years of age)	Observational data from the US CF Registry	**Proposed SmPC text:** **Section 4.1** Cayston is indicated for the suppressive therapy of chronic pulmonary infection 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 and adolescents (i.e. patients < 18 years) as the safety and efficacy of the medicinal product has not been fully established in this patient population.
Tumours, including C-cell adenomas	Regular analysis of postmarketing safety data The possibility of conducting further nonclinical mechanistic studies will be investigated.	**Proposed SmPC text:** **Section 5.5** A 104-week rat inhalation toxicology study to assess the carcinogenic potential of ascending doses (31, 56 and 120 mg/kg/day) of Cayston demonstrated no drug-related increase in malignant tumours. The only evidence of Cayston-related carcinogenicity was a small increase in the incidence of C-cell adenomas in females at 120 mg/kg/day. The clinical relevance of this effect is unknown. No such added effect

		was observed was observed at 56 mg/kg/day in which exposures exceeded 2.2 to 9 times the human exposure, based on AUC or C_{max} respectively.
Important Missing Information		
Limited safety data in adults (including long term safety)	Regular analysis of postmarketing safety data Review of safety data in the following clinical studies and expanded access programs: CP-AI-006 GS-US-205-0110 GS-US-205-0117 EA-US-205-0111 EA-US-205-0122 (Planned study) Observational data from the US CF Registry	N/A
Limited safety data in children	Regular analysis of postmarketing safety data Review of safety data in the following clinical studies, expanded access programs and observational studies: CP-AI-006 GS-US-205-0110 GS-US-205-0117 EA-US-205-0111 EA-US-205-0122 (Planned study) Observational data from the US CF Registry In addition, a review of all pediatric data from controlled studies will be conducted.	N/A
Genotoxicity information (on impurities)	Nonclinical studies: Protocol TX-205-2011 Protocol TX-205-2012 Protocol TX-205-2013	N/A
Nonclinical safety pharmacology information	Nonclinical study: PC205-2001	N/A

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.9 Overall conclusions, risk/benefit assessment and recommendation following re-examination

Quality

Taking into consideration the initial data submitted and the additional clarification presented by the applicant before the opinion it can be concluded that the Information on development, manufacture, control of the active substance and the finished product have been presented and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. At the time of the CHMP opinion, there some unresolved quality issue, which will not have an impact on the benefit/risk ratio of the medicinal product. It is important to underline that the previous major outstanding issues regarding the quality of the active substance and finished product have been clarified and resolved.

Therefore, it can be concluded that the quality characteristics of the finished product are adequate and should have a satisfactory and uniform performance in the clinic.

Non-clinical pharmacology and toxicology

As noted in the primary assessment, following high dose of aztreonam lysine, the incidence of C-cell adenomas in the thyroid gland was increased in female rat. The non-clinical concern on the observed C-cell adenoma with its relevance, especially to children, still needs to be adequately addressed. In view of the limitation of the conditional Marketing Authorization to adult population only, the CHMP agrees that this can be addressed as a "Follow-up Measure (FUM)". In addition, the RMP has been updated to include tumour growth, especially C-adenomas, to be closely monitored as part of pharmacovigilance activities.

Efficacy

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 partcipating in these studies could subsequently receive multiple courses of Cayston in an open-label follow-on study (CP-AI-006). Overall, 344 predominantly adult (77%) patients were treated in these studies. Pulmonary function and respiratory symptoms significantly improved from a baseline at day 28 in patients treated with one course Cayston in both placebo-controlled trials.

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. Over six 28-day courses of therapy, measures of pulmonary function (FEV_1), CFQ-R respiratory symptoms scores, and $\log_{10}$ *P. aeruginosa* CFUs 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. Further data are awaited on the long-term efficacy in adult and paediatric patients alike.

Safety

The adverse reactions attributable to Cayston were primarily self-limiting, local effects associated with inhalation of the proposed medicinal product. However, the long-term significance of these findings has not been determined. Further data are awaited on the long-term safety (and resistance data) in adult and paediatric patients alike.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user testing report submitted is adequate and in accordance with current recommendations.

Risk-benefit assessment

Benefits

It is considered that adults represent a significant proportion of the total CF patient population and the vast majority of chronically PA-infected patients. In the main controlled short treatment trials, which included a majority of adult patients, Cayston showed an undisputable improvement on lung function. It is encouraging to note that the treatment effect seemed to persist over various treatment courses. However this has to be interpreted with the caveat that these data were obtained in uncontrolled circumstances and with possible resort to concomitant drugs against *Pseudomonas aeruginosa* (at the investigator's discretion).

It is also considered that the risk of adverse reactions and risk of the development of resistance are acceptable when the duration of treatment is limited to four weeks (one treatment course).

Risks

There are insufficient long-term efficacy and safety data after repeated courses with the product from randomised studies in CF patients with targeted disease. The present data are also insufficient to resolve the raised concerns with regard to the risk of acquired resistance. The results of the ongoing randomised EU Study GS-US-205-0110 are warranted before drawing definitive conclusions with regard to the long-term effects of Cayston.

Also experience is limited in children, warranting further controlled data on short term and long term repeated use in the paediatric population.

Finally, the non-clinical concern on the observed C-cell adenoma and its relevance to patients has not been adequately resolved and will need to be further addressed (FUM).

Balance

The overall risk-benefit ratio for Cayston is considered favourable for a revised indication limited to single treatment course in adult CF patients only.

The data available in children are too limited at present, warranting further data from well controlled trials to support short term and long term repeated use in the paediatric population.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

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

Recommendation following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Cayston in the suppressive therapy of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 18 years and older was favourable and therefore recommended the granting of the conditional marketing authorisation.

A divergent opinion was expressed by a minority, stating the following objections:

- It has not been adequately demonstrated whether the effect observed on respiratory function at 28 days would translate into a sustained benefit over subsequent courses of treatment as required in this chronic disease.

- Whilst it is recognised that there is an unmet medical need for improved outcome in patients with cystic fibrosis, there is currently insufficient information to establish whether Cayston fulfils an unmet medical need in the absence of long term controlled data. Furthermore there is insufficient information on the safety and efficacy of Cayston in the paediatric population, where there is also a clear need for treatments offering improved outcomes.