Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Aztreonam

Proprietary Product Name: Cayston

Sponsor: Gilead Sciences Pty Ltd

March 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Product Details

Type of Submission	New Dosage Form
Decision:	Approved
Date of Decision	2 February 2010
Active ingredient(s):	Aztreonam
Product Name(s):	Cayston
Sponsor's Name and Address	Gilead Sciences Pty Ltd Level 1, 128 Jolimont Road East Melbourne VIC 3002
Dose form(s):	Inhalation
Strength(s):	75 mg
Container(s):	Cayston - Amber Type I glass vials with rubber stoppers. Diluent – LDPE ampoule
Pack size(s):	Each composite pack contains 84 vials of Cayston and 88 ampoules of diluent per carton.
Approved Therapeutic use:	Control of gram-negative bacteria, particularly *Pseudomonas aeruginosa*, in the respiratory tract of patients with cystic fibrosis.
Route(s) of administration:	Inhalation
Dosage:	The recommended dosage regimen is one vial of Cayston (75 mg) administered three times per day for a 28-day course, followed by 28 days off Cayston therapy. Each dose should be taken at least four hours apart.

Product Background

Cystic fibrosis is a rare, 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 glands. In Europe, for example, 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 including *Pseudomonas aeruginosa* (PA), *Burkholderia cepacia* (*B. cepacia*), and *Stenotrophomonas maltophilia* (*S. maltophilia*). The most significant bacterial pathogen associated with CF pulmonary disease is PA. Pseudomonas infections are usually established in the first decade of life. PA infection is a significant predictor of mortality, and has also been associated with higher rates of pulmonary function decline. Once established, these

infections are rarely eradicated despite aggressive antibiotic therapy. Infected patients experience progressive obstruction of the airways and loss of lung function. Loss of pulmonary function is the primary cause of death in patients with CF.

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 PA. There are two main treatment strategies that are widely used for the management of chronic PA lung infection in people with CF: The first approach is giving regular courses of intravenous antibiotics or inhalational antibiotics; the second approach is "on demand", that is, 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). In both cases IV therapy was the mainstay and patients could receive concomitant treatments such as nebulised antibiotics (25-40%), oral anti-staphylococcal antibiotics and regular inhaled bronchodilators in a balanced fashion. "On demand treatment" does not seem to result in a significant reduction in the number of courses of treatment when compared to regular treatment.

Tobramycin Inhalation Solution is currently approved in several countries including Australia and is marketed in the US and EU for the management of CF patients with PA. Despite its proven efficacy, a clinical need exists for another treatment option in aerosol antibiotic therapy. The primary therapy for pulmonary exacerbations is IV tobramycin, and frequent aerosol use of this agent may lead to selective pressure favouring resistant PA strains. Many clinicians are reluctant to use aerosolized tobramycin for chronic suppressive therapy, fearing that long-term exposure could further promote resistance and diminish the effectiveness of IV aminoglycoside therapy.

Cayston is a novel formulation of the antibiotic aztreonam that has been modified to make it more airway-tolerable. Aztreonam is a water soluble synthetic monobactam antibiotic. Cayston is proposed for the control of gram negative bacteria, particularly *Pseudomonas aeruginosa* in the respiratory tract of patients with cystic fibrosis

Regulatory Status at the Time of Submission

A different formulation of the same antibiotic, aztreonam (arginine) for intravenous injection, is approved in Australia for the following indications:

- As a single agent in the treatment of infections known or strongly suspected to be due to susceptible Gram negative aerobes, such as urinary tract infection and gonorrhoea.
- In combination with other suitable antibiotics to treat serious infections due to problem organisms known or likely to be susceptible to aztreonam.
- Meningitis caused by Haemophilus influenzae or Neisseria meningitidis in combination with other antibiotics.

Cayston (aztreonam 75 mg powder for inhalation) was designated as an Orphan Drug by the TGA on 16 July 2007.

Similar applications has been approved in the EU (21 September 2009) and Canada (11 September 2009). The approved indications for the EU are:

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

In Canada, the indications are:

Cayston (aztreonam for inhalation solution) is indicated for the management of cystic fibrosis (CF) patients with chronic pulmonary Pseudomonas aeruginosa infections (see Clinical Trials).

Applications have been submitted to the United States (16 November, 2007), Turkey and Switzerland. In a press release dated 16 September, 2008, the sponsor announced that the US FDA had declined to approve the application and that an additional clinical study will be required. The basis of the decision was not reported, but Gilead noted that there were no safety concerns and that the expanded access program will continue. In a subsequent press release dated 10 December 2009, the sponsor announced that the Anti-Infective Drugs Advisory Committee of the US FDA recommended that Cayston be approved for the treatment of infections due to *Pseudomonas aeruginosa* in patients with CF. The committee voted 15 to 2 that the sponsor had provided sufficient evidence of the safety and efficacy of Cayston.

Product Information

The approved product information current at the time this AusPAR was developed is contained at Attachment 1.

II. Quality Findings

Aztreonam, a monobactam antibiotic, is currently registered by Bristol-Myers Squibb as a 1 gram powder for injection (Azactam). The present application seeks to register a powder for inhalation, containing 75 mg of aztreonam. The powder is reconstituted using a 1 mL ampoule of sterile saline (0.17% w/v sodium chloride) which is supplied with the lyophilised drug product. The resulting solution is administered using a specified nebuliser device that will be evaluated separately by the Medical Devices Assessment Section of the Office of Devices, Blood and Tissues of the TGA.

Cayston is a novel dosage form for the antibiotic aztreonam. Aztreonam is a water soluble synthetic monobactam antibiotic. Cayston is proposed for the control of gram negative bacteria, particularly *Pseudomonas aeruginosa* in the respiratory tract of patients with cystic fibrosis Cayston is to be administered by inhalation after reconstitution with a diluent, using the Altera Nebuliser System (in clinical trials referred to as the PARI eFlow nebuliser device). The device is not part of the medicinal product and needs to be provided separately.

Drug Substance (active ingredient)

Structure

The structure of aztreonam is shown below.

No Structure

Manufacture

The drug substance is produced by chemical synthesis.

Physical and Chemical Properties

Four polymorphic forms of aztreonam exist (α, β, δ and γ) however the manufacturer only produces the α-form, which is a non-stoichiometric hydrate, containing 12-18% water.

Alpha-aztreonam is a white to off-white crystalline powder that is soluble in water with a melting point of 227°C. The dissociation constants (pKa) of aztreonam are -0.7, 2.75 and 3.91 with a Log P partition coefficient value of -0.66. Alpha-aztreonam has been demonstrated to be highly hygroscopic.

Specifications

There is a USP monograph for aztreonam which, until recently, was only relevant to β-aztreonam, which is anhydrous. The monograph has recently been revised to cover both α and β polymorphs. The assay limits in the monograph for the α-form are 92.0 – 105.0% on the anhydrous basis. It is not clear why the assay limits are so broad, given that the manufacturer applies limits of 1.0% for total impurities and 0.1% for residue on ignition. In recognition of this, the manufacturer of Cayston applies assay acceptance limits of 97.0 – 103.0% to the active ingredient, although batch analysis data suggest that the limits could be even tighter (e.g. 98.0 – 102.0%).

The proposed specifications from the finished product manufacturer were reviewed. The drug substance contains two known impurities, described as "open–ring" and the "E-isomer", which are controlled by appropriate limits. The limit for total impurities is also appropriately controlled. Based on batch analysis results generated to date, the company has been requested to tighten all proposed chromatographic purity limits and to tighten the assay limits to 98.0 – 102.0%.

Stability

The drug substance is stable, and adequate data have been provided to support the proposed retest period of 12 months when stored at 5ºC ± 3ºC.

Drug Product

The drug product is a sterile lyophilised powder for reconstitution and inhalation which contains 75 mg of aztreonam and 46.7 mg of lysine as the monohydrate. The product is supplied in a single use 2 mL Type I amber glass vial with a siliconised rubber stopper and an over-seal cap. Each vial is reconstituted with an ampoule containing 1 mL of sterile saline solution (0.17% w/v sodium chloride) which is supplied with the lyophilised drug product. Each composite pack contains 84 vials of Cayston and 88 ampoules of diluent.

The literature documents that the lungs can be damaged by either basic or highly acidic conditions and that the airways can tolerate an aerosolised antibiotic solution having a pH

range from 4.0 to 8.2. With this knowledge, as well as the known solubility/stability constraints of the drug substance, aztreonam, a formulation was developed. An aqueous solution of aztreonam is most stable in the pH range of approximately 4.5 to 6.0 with less degradation observed in this pH range as well as an increase in solubility in the pH range of 4.0 to 7.5. As the drug substance was known to be sensitive to light, an amber glass vial was chosen as the container for commercial manufacture.

Manufacture

Aztreonam and lysine are mixed with Water for Injections and filtered under nitrogen through a 0.22 µm filter. Aztreonam has been shown to be sensitive to temperature with significant levels of degradant products observed above 8°C and as such, gamma radiation and thermal sterilisation methods were not viable options for manufacturing a sterile product.

Specifications

The proposed specifications control identity, assay, purity and other physical, chemical and microbiological properties relevant to the clinical use of the product.

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under in-use, accelerated and real time conditions to characterise the stability profile of the product.

The proposed shelf life for the unopened product is 24 months when stored refrigerated below 8°C which is justified. The secondary shelf life proposes that the product may also be stored for up to 28 days below 25°C and is also justified.

As the product is intended for inhalation via nebulisation after reconstitution with the diluent bioavailability data were not required to be submitted.

Diluent

The diluent for Cayston aztreonam for inhalation (75 mg) is a single use, sterile preservative free, 0.17% w/v sodium chloride solution. The diluent is supplied in a single use 1 mL blow-fill-seal low density polyethylene (LDPE) ampoule.

The concentration of sodium chloride was selected to create an osmolality of the final reconstituted solution not exceeding 550 mOsm/kg. Osmolality is a critical parameter for consideration in the prevention of bronchospasm and coughing when the reconstituted drug product is inhaled into the lungs.

The specifications were reviewed. 'Deliverable volume' or the volume of diluent contained in the ampoule is monitored in the specification as a measure of control of the osmolality of the reconstituted drug product solution, within the airway tolerability range of 150-550 mOsm/kg. Sodium chloride is the only component in the diluent which contributes to the osmolality of the reconstituted drug product. Therefore, monitoring the volume of diluent ensures minimal sodium chloride concentration changes and as a consequence, minimal change in the osmolality of the reconstituted drug product.

Stability data have been generated under accelerated and real time conditions to characterise the stability profile of the product. The proposed shelf life of 3 years when stored below 25°C for the unopened product is justified. The alternate proposed shelf life of 3 years when stored under refrigeration below 8°C (when the diluent is packaged with Cayston vials) is also justified.

Quality Summary and Conclusions

This application was referred to the 123rd meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) on 24 November 2008. The PSC supported the questions that had been raised by the TGA, particularly the request to lower the pre-filtration bioburden limit to a more widely accepted value, during manufacture of the product. Eventually, the TGA accepted a limit on the basis that data are available for only a limited number of raw material lots at this time.

The PSC also requested that information be provided on shipping conditions and temperature monitoring during shipping of the drug substance, which must be stored under refrigeration. This has been brought to the sponsor's attention.

All other matters raised with the sponsor have been satisfactorily addressed. On chemistry and quality control grounds, there are no objections to registration of this product. However, it is noted that the Drug Toxicology Evaluation Section considers that the five impurities specified in the drug substance and finished product specifications have not been adequately qualified at the limits proposed. This matter should be resolved prior to registration approval.

III. Nonclinical Findings

Introduction

Gilead Sciences Pty Ltd has applied to register a new formulation of aztreonam under the trade name Cayston. Aztreonam is a monobactam antibiotic currently registered by Bristol-Myers-Squibb Australia Pty Ltd for the parenteral treatment of Gram negative bacterial infections. The current submission by Gilead Sciences Pty Ltd is for a novel formulation to allow delivery of aztreonam via inhalation (AI) to patients with cystic fibrosis (CF). The proposed formulation differs from the previously registered aztreonam formulation in that it possesses L-lysine in place of L-arginine.

Based on the pharmacokinetics of intravenously (IV)-administered formulations in dogs, the systemic kinetics of the new formulation of aztreonam-lysine was similar to the previously-registered aztreonam-arginine. Therefore the toxicity data submitted previously for aztreonam-arginine are valid for evaluation of the systemic toxicity of the new formulation.

In support of the current application, aztreonam pharmacology, reproductive toxicology and genotoxicity from the previous registration application by Bristol-Myers-Squibb Australia Pty Ltd were submitted. Throughout this evaluation report, aztreonam-lysine and aztreonam-arginine, are considered synonymous in terms of toxicity profiles and are referred to as "aztreonam". Exceptions to this are noted where appropriate.

The current submission consisted of a number of repeat-dose studies in rats and dogs and a rat carcinogenicity study with aztreonam. All studies were performed using the inhalation route with standardised dosing methods. Two local tolerance studies and an inflammatory response study were performed. All of these studies were conducted according to Good Laboratory Practice (GLP) principles, and toxicity studies were supported by toxicokinetic data.

Pharmacology

Primary pharmacodynamics

Aztreonam is a monobactam antibiotic which binds to the penicillin binding protein (PBP3) of aerobic Gram-negative bacteria, including *Pseudomonas aeruginosa*, resulting in filamentation and cell lysis. An antibiotic risk assessment was submitted by the sponsor but this was not evaluated in the main body of this report.

Efficacy

The minimal inhibitory concentration (MIC) range for aztreonam on *P. aeruginosa* has been reported to be 0.2-50 µg/mL in 1982 (Sykes *et al.*, 1982) and ≤2-2048 µg/mL in 2006 (Gibson *et al.*, 2006). According to the EUCAST website the antibiotic susceptibility breakpoint is 16 µg/mL.[1] There was considerable variability in sputum levels in cystic fibrosis patients that had received Cayston; however sputum levels of aztreonam were on average 20-fold the susceptibility breakpoint and up to 2-fold the MIC_{90} for *P. aeruginosa* strains reported for the study. However, aztreonam is rapidly cleared from the lung with a half-life of approximately 1 hour. The sputum concentrations at 4 hours were at or above the susceptibility breakpoint. As treatment occurs every 8 hours (75 mg three times daily), the sputum concentrations are likely to be higher than the MIC for approximately half of the treatment period. As there were no efficacy studies performed in nonclinical models of infection, evidence of antimicrobial efficacy will depend on clinical data.

Antibiotic resistance risk assessment

[1] http://www.srga.org/eucastwt/MICTAB/index.html, 2008

There have been several reports of aztreonam resistance development in *P. aeruginosa*. In the Azactam application the MIC of aztreonam for *P. aeruginosa* reportedly increased from 1.2 µg/mL to 100 µg/mL after 8 passages in sub-inhibitory concentrations of aztreonam. The most common mechanisms of resistance in *P. aeruginosa* include the expression of the β-lactamase, *ampC*, which can be either chromosomal or plasmid-encoded, a decrease in porin synthesis and increased efflux activity (Quale *et al.*, 2006). These resistance mechanisms may be chromosomally-encoded and may occur spontaneously. Of concern is that the increase in resistance to aztreonam by any of these means correlates with an increase in resistance to other β-lactams such as ceftazidine, cefoperazone, cefsulodin, piperacillin, ticarcillin and carbenicillin (Chow *et al.*, 1989). However, there are no reports of cross-resistance with other classes of antibiotics such as aminoglycosides (for example tobramycin) and quinolones (for example ciprofloxacin). The chromosomally-encoded resistance mechanisms of increased efflux activity or decreased porin synthesis are not likely to be easily transferred to other bacterial species. However, a plasmid-encoded *ampC* gene has been shown to be transferred to other bacterial species such as *E. coli* and *Klebsiella pneumoniae* (Pitout *et al.*, 1997).

Therefore, *in vitro* studies have demonstrated that *P. aeruginosa* has the ability to acquire aztreonam resistance which would correlate with an increase in resistance to other β-lactams, but not other classes of antibiotics. The risk of transfer of resistance to other bacteria is low but possible. Cayston is intended for prolonged use and the development of resistance is likely. However, the dosage regimen chosen has been designed to delay resistance development in *P. aeruginosa*.

Pharmacokinetics

The systemic bioavailability of aztreonam after inhalation was low (4-23%; Table 1). The relative bioavailability was lower (about 70%) in cystic fibrosis (CF) patients than healthy subjects (Table 1). This is probably due to poor absorption through the fibrotic lung, resulting in lower systemic exposures. However, local concentrations of aztreonam are more relevant to antimicrobial efficacy than systemic concentrations, whilst both concentrations are toxicologically-relevant.

Though low systemic exposures (relative to IV administration) were observed after inhalation of aztreonam, high local concentrations were observed in the sputum of CF patients, with the maximum sputum levels 1200-fold the serum C_{max} value and sputum exposures approximately 960-fold the systemic exposure. As the half-life of aztreonam in the sputum was approximately 1 hour, the sputum concentrations are likely to be higher than the MIC of aztreonam for *P. aeruginosa* for approximately half of the treatment period (see *Primary Pharmacodynamics*), an important consideration for clinical efficacy.

As stated in the clinical section, the half-life of aztreonam in the sputum of CF patients was approximately 1 hour with a concomitant rise in serum levels, suggesting rapid absorption. No apparent accumulation in the lungs was reported upon repeat dosing up to 14 days. No apparent pulmonary metabolism was observed *in vitro* using rat, dog and human pulmonary microsomal fractions, suggesting no first-pass metabolism. Therefore, after inhalation, absorbed aztreonam should behave systemically similar to IV-administered aztreonam and be excreted from the body in the urine. Toxicity data submitted for Azactam would be relevant to toxicity due to systemically-absorbed aztreonam-lysine.

Table 1**:** Relative bioavailability of inhaled aztreonam in relevant species

	IV	**IH**	**Bioavailability[a]**
Rats			
Dose (mg/kg)	25	30	17%
AUC_{0-t} (µg.h/mL)	44[b]	8.8[c]	
Reference	Migdalof *et al.* (1986)[2]	Study NC 664348	
Dogs			
Dose (mg/kg)	20	35	4%
AUC_{0-t} (µg.h/mL)	81.9[c]	5.74[c]	
Reference	Study NC 6169	Study NC 664353	
Humans (healthy)			
Dose (mg/kg)	6.6[e]	4.07[f]	23%
AUC_{0-t} (µg.h/mL)	64.0[b]	9.2[d]	
Reference	Swabb *et al.*(1983)	Study CP-AI-001	
Humans (CF patients)			
Dose (mg/kg)	36.4[g]	1.11[h]	16%
AUC_{0-t} (µg.h/mL)	336.7[b]	1.63[b]	
Reference	Vinks *et al.* (2007)	Study CP-AI-002	

[a]$F = (AUC_{IH}*dose_{IV})*100/(AUC_{IV}*dose_{IH})$; [b]t = 8 h; [c]$t = \infty$; [d]t = 24 h; [e]500 mg dose to a population with average weight of 75.3 kg; [f]285 mg dose to a population with average weight of 70 kg; [g]2000 mg to a population with average weight 54.9 kg; [h]75 mg to a population with average weight 67.4 kg. IV = intravenous, IH= inhalation

Pharmacokinetic drug interactions

No enzyme induction studies were performed, but an analysis of the literature revealed repression of the CYP3A4 isozyme in male cynomolgus monkeys (Ohmori *et al.*, 1994), suggesting aztreonam has the potential to alter the plasma concentration profiles of concurrent drugs. However, CYP3A4 isozyme repression in monkeys occurred at doses ≥ 40 mg/kg/day IV-administered aztreonam, which is approximately 16 fold the recommended dose of aztreonam administered by inhalation, based on body surface area[3] and there have been no reports of drug interactions with aztreonam that could be attributed to effects on CYP3A4 levels. Therefore these findings are not likely to be clinically-relevant and there are insufficient grounds to warrant inclusion of this information in the product information (PI) document.

[2] Migdalof, B.H. (1986) Aztreonam: disposition and pharmacokinetics in rats, dogs and monkeys. *N. J. Med.* Spec No: 16-19.

[3] Assuming 3 x 75 mg aztreonam per day to a 50 kg individual, the daily dose would be 4.5 mg/kg or 148.5 mg/m^2 based on body surface area (BSA; conversion factor of 33) by inhalation. As there is approximately 20% bioavailability (Table 1), this would be equivalent to a 29.7 mg/m^2/day IV dose. A 40 mg/kg/day IV dose in monkeys is equivalent to a dose based on BSA of 480 mg/m^2/day, using a conversion factor of 12. This is approximately 16 fold the clinical dose of aztreonam based on BSA.

Relative exposure

Toxicological effects from both local and systemic exposures of aztreonam were examined in nonclinical studies. As local pulmonary exposures do not consistently correlate with systemic exposures in nonclinical species due to species-specific physiological differences, separate systemic and local exposure calculations were performed for interspecies comparisons.

Systemic exposure data from healthy patients treated at the recommended dose were not provided, and therefore could not be used for comparative purposes. A clinical kinetic study was performed at the clinical dose of 75 mg in cystic fibrosis (CF) patients. However, in this study, treatment occurred only once daily rather than the intended frequency of three times daily. Therefore, for comparative purposes with nonclinical kinetic data, the systemic exposure over 8 hours ($AUC_{0\text{-}8\ h}$ = 1.5 µg.h/mL) in CF patients from a 75 mg dose was used but extrapolated to an $AUC_{0\text{-}24\ h}$ by three fold multiplication (that is, 4.5 µg.h/mL) (Table 2). The systemic bioavailability in CF patients was about 70% relative to healthy subjects (Table 1) and therefore exposure multiples would be expected to be marginally lower if data from healthy subjects were used for comparison, but CF patient data are more relevant for the proposed clinical indications.

For simplicity, the systemic exposure ratio is referred to as SER_{AUC} and the local (alveolar) exposure ratio is referred to as LER. Doses used in all of the studies resulted in exposures that were either equal to or greater than the expected exposure in humans. The No Observable Adverse Effect Level (NOAEL) for each of the studies is noted in **bold-face**.

Table 2**.** Pharmacokinetic/toxicokinetic summary data for rats and dogs (systemic exposure).

Species	Study No.	Study duration	Mean achieved doses (mg/kg/day)	Plasma $AUC_{0\text{-}\infty}$ (µg.h/mL)	Systemic exposure ratio[a] (SER_{AUC})
Rats	NC 663559	28 Days	37.5, 75.5, **157**	7.4, 16, **31**	2, 4, **7**
	NC 668117	28 Days	**119**	**33**	**7**
	NC 664348	90 Days	**32**, 62, 122	**7.5**, 18, 36.5	**2**, 4, 8
Dogs	NC 663496	28 Days	53, 95, **178**	10, 24, **70**	2, 5, **16**
	NC 664353	90 Days	34, 73, **134**	6.2, 18, **32**	1, 4, **7**

[a]The relative exposure was determined using the AUC from Report CP-AI-002 where CF patients were treated with 75 mg and the recommended dosage is 75 mg tds ($AUC_{0\text{-}24\ h}$=3x $AUC_{0\text{-}8\ h}$=3x1.5 µg.h/mL=4.5 µg.h/mL).

No nonclinical data were obtained to determine drug concentrations in the alveolar lining fluid. However, an indication of the relevance of nonclinical studies on local toxicological effects can be estimated based on alveolar surface area and approximate alveolar deposition rates. Local exposure comparisons based on inhalation studies depend on species-specific determinants of deposition and retention of inhaled particulate compounds (Oberdörster, 1991). Retention of the particles is dependent on the aerodynamic diameter of the aerosol particles and the pulmonary dynamics of each experimental animal (Leong *et al.*, 1998). All of the studies, except one, used aerosols that were greater than 80% respirable for their respective species. Doses used in all of the studies resulted in pulmonary exposures that were greater than the expected exposure in humans (Table 3).

Animals were only dosed once daily, relative to a clinical regimen of three times daily, due to limitations on the maximum solution concentration (100 mg/mL) and the maximum duration

of exposure permitted by the Animal Care and Use Committee of the test laboratory (4 hours for rats and 1 hour for dogs). Given that the serum half-life of aztreonam is 1-2 hours in rats, treated animals were not exposed to aztreonam for a substantial period of each day, with undetectable levels of aztreonam in the serum 8 hours after dosing. Nonetheless, multiples of the clinical exposure (AUC) were achieved in rat toxicity studies. In dogs, the serum half-life was longer than in humans (> 5 hours compared with 2-3 hours) and multiples of the clinical systemic exposure were also achieved.

Table 3: Estimated lung exposure data for rats and dogs.

Species	Study No.	Study duration	Mean achieved doses (mg/kg/day)	Estimated lung exposure (mg/m^2/day)	Local exposure ratio[a] (LER)
Rats	NC 663632	7 Days	**34**, 144	**3.2**, 13.4	**4**, 17
	NC 663559	28 Days	37.5, 75.5, **157**	3.4, 7.0, **14.6**	4, 9, **18**
	NC 668117	28 Days	**119**	**12.4**	**16**
	NC 664348	90 Days	**32**, 62, 122	**3.0**, 5.8, 11.3	**4**, 7, 14
	NC 665137	104 Weeks	31, **56**, 120	2.9, **5.2**, 11.2	4, **7**, 14
Dogs	NC 663496	28 Days	53, 95, **178**	2.9, 5.2, **9.8**	4, 7, **12**
	NC 664353	90 Days	34, 73, **134**	1.9, 4.0, **7.4**	2, 5, **9**

[a]The relative exposure was determined using a local exposure determination from 75 mg aztreonam administered tds – 0.79 mg/m^2/day, according to the formula in Appendix 2.

Toxicology

The submitted studies included inhalation (IH) studies in rats and dogs over various durations from 7 days to 90 days or 104 weeks (in the carcinogenicity study). Treatment-related effects were observed in several organs or systems. A comparison of the treatment-related effects observed in the previous submission of intravenously (IV) (or subcutaneously, SC) administered aztreonam with those observed in the 3-month inhalation studies is shown in Table 4. In both the IV/SC and IH studies, treatment-related effects were observed on the kidney (including changes in urine parameters), the liver and the endocrine system, such as the adrenal glands, thyroid gland and pituitary gland. These findings are considered to be a result of systemic exposure to aztreonam and will be discussed in that context. New histopathological findings identified in the IH studies included changes in the lungs, the olfactory epithelium and the larynx. These are considered local effects due to the IH administration method. The relevance of these effects in nonclinical species to humans is discussed below in light of differences in breathing during administration (nasal versus oropharyngeal) as well as differences in the anatomy of the respiratory tract between nonclinical animals and humans.

Table 4: Summary of consistent findings in either rats or dogs that had received aztreonam intravenously/subcutaneously (SC) or via inhalation (IH).

	SC		IH	
	Rats	**Dogs**	**Rats**	**Dogs**
Haematology				
Neutrophils	↑ (non-spec[a])		↓	↓
Systemic effects				
Biochemical changes				

	SC		IH	
	Rats	**Dogs**	**Rats**	**Dogs**
Serum cholesterol		↑		
Bilirubin (serum)			↓	↓
Urinary pH	↓	↓	↓	
Urine Na		↓	↓	
Urine creatinine			↑	
Organ weights				
Kidney	↑	↑		
Liver	↑	↑		
Ovary	↑			
Adrenal gland	↑		↓	
Thyroid gland	↑		↑	↑
Pituitary gland	↑			
Thymus	↓			↑
Histopathology				
Liver				
haemosiderosis in liver	√			
cellular hypertrophy		√		
eosinophilic cell focus			√	
Kidney				
tubular degeneration	√			
cellular vacuolation	√	√		
pelvic mineralisation			√	
Local effects				
Organ weights				
Lungs				↑
Histopathology				
Lungs				
perivascular MN cell			√	
inflammation				√
Nasal cavity				
Epithelial atrophy			√	
Rhinitis			√	
Eosinophilic globules			√	
Larynx				
squamous metaplasia			√	

[a]non-spec – non-specific or secondary to subcutaneous haemorrhage at the injection site.

Systemic toxicity

The dosing regimen for aztreonam (Azactam) is 2 g every 6 or 8 hours, with a maximum total of 8 g/day, intravenously or intramuscularly. The current submission for Cayston proposes a dosing regimen of 75 mg three times daily (tds) via inhalation with a total of 0.225 g/day. The new dosing regimen therefore consists of approximately 36 times [0.225 compared with 8 g/day] less aztreonam than the previous recommended dose. With about 20% systemic bioavailability of inhaled aztreonam (Table 1), the proposed dosing of 75 mg tds aztreonam via inhalation (AI) would result in an estimated systemic exposure of aztreonam 180-fold lower than the currently-registered formulation Azactam. Therefore, previous studies as well as newly-submitted studies included in this application should provide a comprehensive indication of the systemic toxicity of aztreonam.

Renal and hepatic toxicity

The two target organs for toxicity in the previous submission were the kidneys and the liver. The renal effects observed previously included tubular degeneration and cellular vacuolation, with a No Observed Effect Level (NOEL) in rats of 150 mg/kg/day SC and dogs, 50 mg/kg/day SC. Based on the anticipated systemic exposure, lower dose and poor systemic bioavailability *via* inhalation, these doses are estimated to have SER_{AUC} = 1092 for rats and 312 for dogs. Whilst there were several biochemical indicators of perturbations to the renal system in response to aztreonam treatment (Table 4), histopathological changes (pelvic mineralisation) were only observed in a single study (rat carcinogenicity study; NOEL < 30 mg/kg/day, SER_{AUC} = 1-2). This suggests that only mild renal effects occurred in the nonclinical studies, most likely as a result of the active tubular excretion of aztreonam (Mattie, 1994) which is largely excreted in the urine unchanged. The potential nephrotoxicity of aztreonam is low (1% of administered patients treated with 6 g/day IV, that is, 135 fold the anticipated exposure with Cayston; Moore *et al.*, 1992) compared with other antibiotics, such as tobramycin. Therefore the renal toxicity safety margin is sufficiently high to be deemed not clinically-relevant.

Along with the kidney, the liver was identified as affected by aztreonam administration in the previous submission. These effects included increased liver weights, cellular hypertrophy, reduced cytoplasmic density and increased glycogen deposition. The NOELs for these histopathological effects were identical to those observed for the renal effects (SER_{AUC} = 1092 for rats and 312 for dogs; see above). Histopathological changes (eosinophilic cell focus) in this application were only observed in female rats in the carcinogenicity study (NOEL < 31 mg/kg/day; SER_{AUC} = 1-2). As histopathological changes in the liver were only observed in a single nonclinical study, no other indications of hepatic dysfunction were observed and no changes in hepatic laboratory results were reported in the clinical trials, the effect of Cayston on the liver is likely to be negligible.

Endocrine system

Thyroid-pituitary gland system

An increase in thyroid weights was observed in most rat studies, with a SER_{AUC} as low as 2 when rats were treated daily for 90 days. The increased weights were rarely associated with histopathological findings, except in the carcinogenicity study in which diffuse C-cell hyperplasia was observed in females that had received 31 mg/kg/day aztreonam and males that had received 120 mg/kg/day for 104 weeks. No toxicokinetic data was obtained in this study but based on other studies this dose would correspond to a SER_{AUC} of 2 and 8 for females and males, respectively. An increase in the incidence of thyroid C-cell adenoma was evident in female rats that had received 120 mg/kg/day (SER_{AUC} = 8), but not 56 or 31 mg/kg/day. An increase in the incidence of focal hypertrophy was also evident in the pituitary glands of males that had received 56 mg/kg/day (SER_{AUC}= 4) aztreonam daily for 104 weeks.

Thyroid/pituitary gland histopathological changes were not reported in the previous submission of Azactam, although increases in the relative organ weights of the pituitary and thyroid glands in rats had been observed (Table 4). The absence of histopathological changes in the previous submission is most likely a result of an absence of long term studies (the longest study was 6 months).

Most chemicals that cause thyroid tumours do so as a result of perturbation of the thyroid-pituitary hormone status (Hill *et al.*, 1998). This can occur as a result of increased metabolic degradation of thyroid hormone (either T_3 or T_4) due to the increased expression of thyroid

hormone degrading enzymes, CYP1A and CYP2B (van der Ven *et al.*, 2008; Maglich *et al.*, 2004). Activities corresponding to these cytochrome P450 enzymes were increased in female rats that had received aztreonam (40 mg/kg/day IV; Horie *et al.*, 1987). This would correspond with approximately 200 mg/kg/day if administered by inhalation (based on 20% bioavailability), and therefore similar to the level in female rats that resulted in thyroid adenoma formation (120 mg/kg/day). Though no P450 induction studies were performed with the proposed formulation and administration route, based on published data, P450 induction is possible in rats. The increased induction of these enzymes, would correspond with increased thyroid hormone degradation leading to increased thyroid stimulating hormone (TSH) stimulation of thyroid gland follicular cells. Chronic stimulation of the thyroid by TSH would eventually result in increased thyroid gland weights, hyperplasia and potentially neoplastic formations (Hill *et al.*, 1998; see *Genotoxicity and Carcinogenicity*).

Rodents are generally more susceptible to perturbations of thyroid-pituitary homeostasis than humans and thyroid cancer formation in rodents is generally not clinically relevant (Hill *et al.*, 1998). Therefore the risk of thyroid tumour formation with the current formulation and dosing regime is considered low.

Adrenals/Prostate/Thymus

Focal cortical cell hyperplasia or hypertrophy in the adrenal gland was observed in rats (treated daily for 104 weeks, SER_{AUC}= 4) and in dogs (treated daily for 90 days, SER_{AUC}= 4). As this hyperplasia/hypertrophy occurred in the zona fasciculata it suggests a possible imbalance in cortisol synthesis. This could be as a result of impairment of biosynthetic regulation by the pituitary-secreted adenocorticotropic hormone or a decrease in the expression of cortisol biosynthetic enzymes (van der Ven *et al.*, 2008). Aztreonam was shown to repress the levels of some cytochrome P450 enzymes (see above; Horie *et al.*, 1987). Several steps of the cortisol biosynthetic pathway are shared with androgen biosynthesis. If the effect of aztreonam on cortisol levels also affected androgen levels, such as testosterone, this would explain the affects of aztreonam on the prostate and thymus. A reduction in testosterone levels relative to oestrogen levels may promote cell growth in the prostate gland (Shibata *et al.*, 2000). Likewise a reduction in cortisol levels can result in an increase in thymic weight (Tabarin *et al.*, 1995). However, in the absence of P450 induction data and any direct effect of inhaled aztreonam on endocrine hormone levels, these explanations are purely speculative. As the effects were observed at sufficiently high exposure multiples and due to species differences in the endocrine system, these findings are not likely to be clinically-relevant.

Local toxicity

The major differences observed in nonclinical studies performed on aztreonam administration via inhalation (AI) compared with IV are local effects on the lungs, olfactory epithelium and the larynx.

Lungs

A number of observations were noted regarding changes in the pulmonary system; however, there were no consistent findings that could be attributed to the treatment. In one rat study in which animals were treated for 28 days with 119 mg/kg/day (LER= 16), there was an increase in the incidence of perivascular mononuclear cell infiltration, which may be an indication of inflammation. Darkened lungs and a decrease in alveolar foamy macrophage accumulation were observed in rats that had been treated with aztreonam daily for 104 weeks (LER= 14; NOEL 56 mg/kg/day, LER= 7). However, in light of a lack of pulmonary histopathological findings in other rat studies, the significance of this finding is uncertain.

In both dog inhalation studies, changes were observed in the lungs. Increased relative lung weights and inflammation were observed after daily treatment for 90 days (NOEL 73 mg/kg/day, LER= 5) and 28 days (LER= 5), respectively. However, these findings failed to reach statistical significance. No differences in lung weights or histopathological findings were observed after treatment-free periods. No hyperplastic lesions were observed and therefore local effects on the lungs during clinical administration are unlikely.

Nasal cavity

Changes in the nasal cavity of rats were observed after exposure to inhaled aztreonam. These changes included olfactory epithelial atrophy (NOEL 32 mg/kg/day, LER= 4) and eosinophilic globules in the recovery period (NOEL < 122 mg/kg/day, LER< 14). These nasal cavity changes are most likely due to deposition of test material in the nasopharyngeal region, leading to an inflammatory response. Greater particle deposition occurs in the upper respiratory tract of rats compared with humans during inhalation studies (as only 10% is deposited in the alveolar region compared with 50% for humans) due to the greater complexity of the rodent nasal passages, further exacerbated by the fact that rats are obligate nose-breathers (Dahl *et al.*, 1991). As the intended human administration of AI is through the use of a mouth nebuliser, the nasal cavity effects observed in the nonclinical studies have limited clinical relevance.

Larynx

Laryngeal squamous metaplasia was observed in the majority of the rat inhalation studies in response to treatment (NOEL 37.5 mg/kg/day, LER= 4). No dose-related alterations in the larynx were observed in the dog inhalation studies. Squamous metaplasia of the larynx is commonly observed in rodent inhalation studies and is considered an adaptive response of the respiratory mucosa to chronic irritation and is "not a relevant toxicologic endpoint" (Osimitz *et al.*, 2007). With an absence of findings in the dog inhalation studies and no adverse reports in the clinical trials, these laryngeal findings are likely to be not relevant to clinical administration.

Genotoxicity and carcinogenicity

Genotoxicity tests with aztreonam were performed previously. Aztreonam was non-genotoxic using a mouse lymphoma forward mutation assay and chromosomal aberration assays. Due to the anti-bacterial nature of aztreonam bacterial mutation assays were not practical to perform.

A carcinogenicity study was not submitted with the previous application. For this application, a single rodent carcinogenicity study was submitted. An increased incidence of thyroid C-cell follicular adenomas was observed in female rats that had received 120 mg/kg/day aztreonam for a period of 104 weeks. This is an estimated systemic exposure ratio of 8, based on toxicokinetic data with a NOEL of 56 mg/kg/day (estimated SER_{AUC} = about 4). Therefore a NOEL, and hence an exposure margin, was established for tumourigenicity. Chemicals that result in thyroid tumours generally exert their affect by perturbations of the pituitary-thyroid hormone homeostasis (Hill *et al.*, 1998). This is most likely the case here, whereby TSH stimulation of thyroid gland cells results in hyperplasia and eventually neoplasm formation (see *Systemic toxicity*). As aztreonam is non-genotoxic, neoplasms have probably arisen due to increases in cell division leading to an increase in the overall chance of a spontaneous initiating mutation occurring (Hill *et al.*, 1998). Perturbations of thyroid-pituitary hormone homeostasis in rodents are generally not clinically-relevant (Hill *et al.*, 1998).

Reproductive toxicity

A comprehensive set of reproductive and developmental toxicity studies including fertility, teratology and postnatal development studies was submitted for the previous application. Systemic exposures were sufficiently high to assess the reproductive toxicology of the new formulation.

In the previous submission, aztreonam was shown to cross the placenta, but no drug-related variations or malformations were observed in aztreonam-treated rats or rabbits. There were no observed effects on fertility in either F_0 or F_1 generations. There was a dose-dependent reduction in the viability of the offspring during lactation and a slight difference in maze-learning ability in male pups from treated dams. The NOELs for these effects were estimated to be > 30 fold the anticipated exposure of aztreonam from inhalation and therefore are not likely to be clinically-relevant. The proposed Australian Use in Pregnancy Category of B1 is appropriate.

Although aztreonam has been shown to be excreted in breast milk of healthy human subjects, the concentration excreted was less than 1% that in human serum (Fleiss *et al.*, 1985). Based on low systemic concentrations of aztreonam after inhalation, and postnatal effects occurring at doses greater than 30 fold the anticipated exposure, there are unlikely to be clinical concerns during lactation. However, to remain cautious, a statement about breast milk excretion has been included in the PI document.

Local ocular and dermal tolerance and tracheal sensitisation

The potential of aztreonam to induce ocular or dermal irritation was examined in New Zealand White (NZW) rabbits. No irritation was observed in the eyes treated with 10 mg aztreonam (100 µL of a 100 mg/mL solution). No dermal irritation was observed when animals were treated with 50 mg of aztreonam (0.5 mL of 100 mg/mL).

The potential of aztreonam to induce an allergic response as measured by acute airway obstruction and/or pulmonary eosinophilia following intratracheal administration was evaluated in guinea pigs using 10 mg aztreonam (100 µL of a 100 mg/mL solution). Under the conditions of this study, at levels calculated to be approximately five times the estimated clinical dose (75 mg), aztreonam-sensitized and challenged guinea pigs did not exhibit evidence of the production of reaginic antibodies which would elicit an allergic response.

Excipients

The only major excipient in the formulation is lysine which is present at 1.9 moles per mole of aztreonam, resulting in a proposed dose of 157.5 mg L-lysine per day via inhalation. Lysine was present in all chronic toxicity studies, including the carcinogenicity study, and therefore has been adequately tested in these studies. There were no findings in these studies that could be attributed to the presence of lysine. Based on information contained in the literature, lysine is unlikely to accumulate in the lungs and the amount contained in Cayston is unlikely to promote infectious bacterial growth in the sputum of CF patients. Lysine is non-teratogenic and is unlikely to affect reproductive parameters (van Maele-Fabry-Picard, 1987; Flodin, 1997). Although the amount of lysine in Cayston is 1.9 moles per mole of active pharmaceutical ingredient, the amount of lysine in the recommended human daily dose is unlikely to be of toxicological concern.

Impurities

Impurities were also evaluated for toxicological significance.

Nonclinical Summary and Conclusions

There were no animal studies of inhaled aztreonam lysine in the treatment of pulmonary *P. aeruginosa* infection and therefore evidence of efficacy will depend on clinical data.

Aztreonam for inhalation has been investigated in an adequate range of toxicology studies in relevant animal species.

The systemic toxicity profile of AI was generally similar to that seen with the previously registered aztreonam formulation. However, human systemic drug exposure is substantially lower with the proposed inhaled dose regimen.

Systemic toxicological effects were observed in the kidney, liver and endocrine system. The former two organs were considered targets of aztreonam toxicity in the previous submission. Histopathological effects in the adrenal glands, thyroid glands and pituitary glands were observed in the 2 year carcinogenicity study in rats. Thyroid C-cell hyperplasia was observed in females and males treated with 30 mg/kg/day (systemic exposure ratio of 2) and 120 mg/kg/day (systemic exposure ratio of 8), respectively. Focal hypertrophy in the pituitary glands was also observed in males treated with 60 mg/kg/day with a systemic exposure ratio of 4. Adrenal cortical cell hyperplasia or hypertrophy was observed in rats treated daily for 104 weeks (with a systemic ratio of 4) and in dogs treated daily for 90 days (with a systemic exposure ratio of 4).

A significantly increased incidence of thyroid C-cell follicular adenomas was observed in female rats that had received 120 mg/kg/day aztreonam by inhalation for a period of 104 weeks; the NOEL was 56 mg/kg/day, estimated to be 4-fold the clinical systemic exposure. This correlated with an increase in thyroid C-cell follicular hyperplasia. The clinical relevance of these tumours is considered minimal due to species differences in thyroid homeostasis.

Local toxicological effects were observed in the lungs, nasal cavity and larynx. Pulmonary effects (darkened lungs, inflammation and increased lung weights) were observed in both rats and dogs at local exposure ratios of 14 and 5, respectively. However, these were not always consistent findings in repeat dose studies and failed to reach statistical significance. Therefore local effects on the lungs during clinical administration are unlikely.

Olfactory epithelial atrophy and laryngeal squamous metaplasia were observed in the rat inhalation studies with a local exposure ratio of 4 at the NOEL. As aztreonam will be administered via a mouth nebuliser, the nasal cavity effects observed in the nonclinical studies are not relevant for clinical administration. Laryngeal squamous metaplasia is common in rodent inhalation studies and is considered an adaptive, not a toxicologic response.

An increase in thyroid C-cell adenomas was observed in female rats treated with 120 mg/kg/day aztreonam with a NOEL 4 fold the anticipated clinical exposure. Due to species differences, the thyroid adenomas are unlikely to have clinical significance.

There are no nonclinical objections to the registration of Cayston for the treatment of *P. aeruginosa* infections in cystic fibrosis patients.

IV. Clinical Findings

Initial Clinical Evaluation

Introduction

During the clinical development program, clinical studies enrolled 286 subjects. The submitted studies included data from:

- 2 Phase 1 pharmacokinetic studies (studies AI-001 and AI-002)
- 1 dose ranging Phase 2 efficacy study (study AI-003)
- 2 pivotal Phase 3 studies of efficacy and safety (placebo controlled studies AI-005 and AI-007 and open label roll-over study AI-006)

Pharmacokinetics

Systemic absorption of aztreonam lysine following inhalation was assessed in the two Phase 1 studies, the one Phase two study and two Phase 3 studies. Pharmacokinetic studies were performed in healthy subjects and subjects with cystic fibrosis. The pharmacokinetics of aztreonam following intravenous administration has been defined previously.

Absorption

Plasma levels were much lower following inhalation compared to known levels following intravenous dosing. Following intravenous doses of 500mg, 1g and 2g, peak levels have been reported as 54 μg/mL, 90 μg/mL, and 204 μg/mL respectively.

In contrast, the mean plasma concentration of aztreonam in studies AI-003, AI-005 and AI-007 one hour following inhalation of 75mg was between 0.588 μg/mL and 0.686 μg/mL. There was a wide variability between subjects in all studies (coefficient of variation 52%-66%). In all studies, the time to maximum concentration (Tmax) was approximately 0.5-2 hours.

It is unlikely that oral absorption contributes to plasma levels, as previous studies have demonstrated low bioavailability following oral administration.

Exposure

There was a wide variability in systemic drug exposure following inhalation of aztreonam lysine. In study AI-001 in 18 healthy subjects, mean $AUC_{0\rightarrow\infty}$ following single inhaled doses of 95mg, 190mg and 285mg was 3618 (standard deviation ± 3024) ng.hr/mL, 6764 (±4953) ng.hr/mL and 9111 (±7951) ng.hr/mL respectively (Table 5).

Table 5: Pharmacokinetic parameter estimates following administration of inhaled aztreonam in healthy volunteers (study AI-001)

Dose	Statistic	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)
95 mg	N[a]	6	6	6	5	5	5
	Mean	521	1.16	2514	3618	2.73	50.25
	SD	482	0.41	2494	3024	0.59	38.91
	CV%[b]	92.5	35.3	99.2	83.6	21.6	77.4
	Median	353	0.99	1495	2292	2.66	41.45
	Min	22.5	0.98	75	1000	2.05	12.78
	Max	1190	2.00	6280	7432	3.57	94.98
	Geom. Mean	284	nc	1247	2591	nc	nc
190 mg	N	6	5	6	6	5	5
	Mean	1400	1.10	6189	6764	2.86	37.52
	SD	1050	0.54	4674	4953	0.96	38.15
	CV%[b]	75.0	49.1	75.5	73.2	33.6	102
	Median	1670	1.00	6913	7589	2.46	25.01
	Min	0.0	0.50	0	0	1.87	15.65
	Max	2610	1.98	11927	12139	4.34	105.3
	Geom. Mean	1330	nc	6048	6792	nc	nc
285 mg	N[a,c]	5	5	5	4	4	4
	Mean	2230	0.74	9207	9111	2.69	131.7
	SD	1800	0.25	6825	7951	0.60	198.3
	CV%[b]	80.7	33.8	74.1	87.3	22.3	151
	Median	2420	0.72	10853	8744	2.81	41.83
	Min	97.2	0.50	516	666	1.86	15.58
	Max	4660	1.00	16940	18292	3.30	427.7
	Geom. Mean	1250	nc	5531	5191	nc	nc

Source: CP-AI-001 CSR Tables 14.2.3.1 to 14.2.3.5 and 14.2.3.7

[a]The elimination rate could not be determined for 2 subjects, therefore the number of observations (N) for K_{el} dependent parameters estimations ($t_{1/2}$, $AUC_{0-\infty}$, and CL/F) for the 95 mg and 285 mg doses were 5 and 4, respectively.

[b] CV% calculated as (SD/Mean)*100.

[c]One subject did not complete dosing and was excluded from the statistical summary.

nc = not calculated.

In study AI-002 in 35 subjects with cystic fibrosis, mean AUC0→∞ follow ing the first 75mg dose was 1629 (±522) ng.hr/mL (Table 6).

Table 6: Plasma aztreonam pharmacokinetics following administration of inhaled aztreonam 75mg in patients with cystic fibrosis (study AI-002)

Statistic	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	CL/F (L/hr)	K_{ab}[a] (1/hr)	$t_{1/2}$[a] (hr)
Mean	419	0.99	1496	1629	51.2	3.1	2.1
SD	155	0.35	495	522	18.7	1.3	0.3
CV%[b]	37.0	35.4	33.1	32.0	36.5	43.2	15.2
Median	426	0.97	1453	1617	46.4	2.9	2.1
Min	198	0.55	786	857	28.9	1	1.5
Max	692	1.98	2456	2592	87.5	6	2.4

Source: CP-AI-002 CSR Table 12-4, N=12
[a] Determined from one-compartmental model.
[b] CV% calculated as (SD/Mean)*100.

Maximum plasma concentrations were 419 (± 155) ng/mL at 1 hour following inhalation of 75mg aztreonam in patients with cystic fibrosis (Table 6). These were similar to plasma concentrations in Phase 2/3 studies (Table 7).

Table 7: Plasma levels following first inhaled dose of aztreonam lysine in Phase 2/3 studies AI-003, AI-005 and AI-007

Study	N	Dose (mg)	Mean ng/mL	SD	CV%
CP-AI-003	37	75 mg BID	686.0	365.0	53.2
	37	225 mg BID	1613.3	832.4	51.6
CP-AI-005	66	75 mg BID	536.9	322.5	60.1
	63	75 mg TID	685.4	456.9	66.7
CP-AI-007	72	75 mg TID	550.4	308.5	56.1

Source: CP-AI-003 CSR Table 20, CP-AI-005 CSR Table 47 and CP-AI-007 CSR Table 45

Following repeated dosing of up to 28 days, there was little evidence of accumulation in the two Phase 3 studies with mean peak concentrations of 588 (±370) ng/mL at following the first dose compared to 653 (±394) ng/mL after 28 days of 75mg dosing (twice daily [bd] and three times daily [tds]) (Table 8). This is consistent with the short observed elimination half life of aztreonam lysine.

Aztreonam concentrations were assessed in sputum in studies AI-002, AI-003, AI-005 and AI-007. Sputum concentrations 10 minutes following inhalation of 75mg aztreonam lysine were highly variable, ranging from 0 to 6010µg/mL (mean 384-984 µg/mL). Mean plasma and sputum concentrations were correlated with dose. There was poor correlation between sputum concentrations and plasma concentrations of aztreonam following a 75mg dose.

Table 8: Plasma concentrations of aztreonam 1 hour following inhalation in studies AI-005 and AI-007 on repeat dosing

Treatment	Visit	Mean	SD	Min	Max	n
Placebo Pooled (N=160)	Day 0	1	15	0	175	141
	Day 14	0	0	0	4	137
	Day 28	0	0	0	0	59
AI 75mg BID (N=69)	Day 0	537	322	0	1390	66
	Day 14	617	308	45	1540	65
	Day 28[a]	-	-	-	-	-
AI 75mg TID (N=146)	Day 0	613	389	0	2920	135
	Day 14	684	369	12	1710	135
	Day 28[b]	653	394	0	1740	68
AI Pooled (N=215)	Day 0	588	370	0	2920	201
	Day 14	662	351	12	1710	200
	Day 28[b]	653	394	0	1740	68

Source: SCP Table 1

[a] Per the CP-AI-005 protocol, data collected through Day 14 only.

[b] Day 28 includes data from CP-AI-007 only.

Distribution

Estimates of the volume of distribution were not performed in studies of inhaled aztreonam. However, previous studies have defined the volume of distribution of aztreonam following intravenous administration as 12.7L, indicating distribution in extracellular fluid. Following intravenous dosing, approximately 56%-71% of the drug is bound to serum proteins.

Metabolism

The metabolism of aztreonam was not studied in the development program. Previous studies following intravenous administration have suggested that aztreonam is predominantly excreted unchanged in urine. An inactive metabolite, SQ 26,992, formed by hydrolysis, is present in small amounts and is also renally cleared. Aztreonam was not a substrate for cytochrome P450 hepatic or pulmonary microsomal enzymes in vitro.

Clearance and Excretion

Mechanisms of Clearance

Aztreonam is primarily excreted unchanged in urine. Previous studies using 14C labeled aztreonam found a metabolite of aztreonam, SQ26,992 comprises 7% of urinary radioactivity. Faecal excretion of unchanged aztreonam accounted for 1% of the dose.
Plasma levels of aztreonam were quantifiable for up to 4 hours following inhalation of 75-285 mg of aztreonam lysine in Phase 1 studies. The mean apparent half life was 2.1-2.85 hours which was similar to that reported following intravenous administration (1.5-2.0 hours).

Pharmacokinetics in special groups

There was high variability between patients in plasma aztreonam doses, which was greater than differences in groups by gender, age and disease severity. A population plasma pharmacokinetic study was not performed. No differences between subgroups were felt to be clinically significant.

In Phase 2 and 3 studies AI-003, AI-005 and AI-007, mean plasma concentrations 1 hour following inhalation of aztreonam lysine were higher in males than females, but the difference was not clinically significant. Plasma levels were lower in the 4 subjects 6-12 years of age receiving 75mg bd aztreonam lysine; concentrations were similar in all other groups, including subjects 6-12 years of age receiving 75mg tds dosing (Table 9).

Table 9: Plasma aztreonam concentrations 1 hour following inhalation in Phase 2 and 3 studies, by age group

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

Source: SCS Tables 5.1.4, 5.1.5, and 5.1.6

Sputum aztreonam concentrations 10 minutes following inhalation were higher in adult subjects (>18 years) (Table 10). Subjects with less severe disease (forced expiratory volume in the first second [FEV_1] >50% predicted) had higher plasma concentrations 1 hour following inhalation of aztreonam lysine. No studies were performed in patients with hepatic and/or renal failure, and patients with renal impairment or abnormal liver function were excluded from clinical studies.

Table 10: Sputum aztreonam concentrations 10 minutes following inhalation in Phase 2 and 3 studies, by age group

Dose (mg) Frequency	Day	Concentration in subjects aged ≥ 6 to ≤ 12 (µg/g) Mean (SD), n	Concentration in subjects aged > 12 to < 18 (µg/g) Mean (SD), n	Concentration in subjects aged ≥ 18 (µg/g) Mean (SD), n
75 BID	0	99.75 (73.89), 2	434.95 (316.03), 20	514.79 (470.71), 78
	7	n/a	410.87 (572.66), 9	365.53 (340.43), 27
	14	298.13 (339.32), 3	609.78 (484.11), 12	725.52 (770.08), 46
225 BID	0	n/a	1469.29 (1175.32), 11	1218.67 (1287.92), 24
	7	n/a	724.22 (617.76), 11	1421.06 (1758.80), 24
75 TID	0	629.20 (1283.38), 12	294.30 (244.56), 18	920.90 (910.42), 102
	14	662.53 (805.09), 10	555.92 (509.56), 16	763.19 (616.82), 92
	28	605.44 (771.00), 8	425.45 (491.61), 8	782.97 (701.68), 47

Source: SCS Tables 5.3.4, 5.3.5, and 5.3.6

Although a dose reduction is suggested following intravenous dosing in patients with renal impairment, the level of exposure following inhalation was felt to be unlikely to be significant to warrant dose adjustment.

Drug Interactions

In vitro studies suggested that aztreonam is not a substrate for hepatic or pulmonary microsomal enzymes. Previous animal studies indicate that systemic aztreonam is associated with a decrease in activity of hepatic microsomal enzymes, but no studies have been performed with drugs metabolized by the cytochrome P450 3A4 pathway. Clinical studies suggest no significant interactions between intravenous aztreonam and other antibiotics, including clindamycin, gentamicin, metronidazole and nafcillin. No drug-drug interaction studies were performed in the development program as systemic drug exposure following inhalation was low.

Summary of Pharmacokinetics

Aztreonam lysine is administered by inhalation using a specific electronic device. The dose selected for clinical studies was aztreonam lysine 75mg bd or tds for 14-28 days.

Systemic exposure following inhalation of aztreonam lysine is much lower than exposure following standard intravenous dosing of aztreonam (500mg-2g).

There was considerable variation between patients in plasma and sputum concentrations following inhalation of aztreonam lysine.

The plasma elimination half life was estimated at approximately 2 hours, consistent with previous studies following intravenous administration. Aztreonam is primarily excreted unchanged in urine.

There were no clinically significant differences in plasma or sputum concentrations of aztreonam by gender, age or disease severity. No dose adjustment is suggested for these groups or for patients with renal impairment.

In vitro studies suggest that aztreonam has a low potential for drug interactions.

Pharmacodynamics

Aztreonam is a synthetic monobactam antibiotic with activity against aerobic gram negative bacteria, including *Pseudomonas aeruginosa* (PA). Aztreonam binds to the penicillin-binding protein PBP3 involved in peptidoglycan cross linking and leads to inhibition of bacterial cell wall synthesis. Aztreonam has a different mechanism of action to the aminoglycosides and may retain activity against tobramycin resistant strains.

The spectrum of activity in vitro includes most gram negative organisms including *enterobacteriacae, Neisseria spp, Haemophilus influenzae* and *Pseudomonas aeruginosa*. Aztreonam does not generally have activity against gram positive organisms, but some strains of *Staphylococcus aureus* are susceptible. The reported proportion of PA strains susceptible to aztreonam varies with the population studied; the MIC50 (the concentration required to inhibit 50% of tested strains), was reported as 2 μg/mL and the MIC90 has been reported as 32μg/mL in patients with cystic fibrosis in the United States.

The intravenous formulation of aztreonam, which contains an arginine salt, is unsuitable for use as an inhaled agent due to local inflammatory reactions. The proposed formulation of aztreonam incorporates a lysine salt. The inhaled route of administration has been used for other antibiotic (tobramycin, colistin) and non-antibiotic (DNase) therapies in cystic fibrosis.

Efficacy

There was one Phase 2 trial (AI-003) and two Phase 3 clinical trials (AI-005, AI-007) (Table 11). In addition, data was presented from an interim analysis of a rollover study (AI-006). All patients had cystic fibrosis with airway colonization or infection with *Pseudomonas aeruginosa* (PA). The placebo-controlled studies used subjective and objective clinical and microbiological endpoints over short durations and had limited power to detect differences in other clinically significant endpoints. Together, they provide evidence of a subjective improvement in respiratory symptoms associated with a small but variable improvement in FEV_1 following 28 days of treatment.

Table 11: Key features of Phase 2/3 studies

	CP-AI-003	CP-AI-005	CP-AI-007	CP-AI-006
Number of patients treated (AI or placebo)	105	211	164	207 at time of interim
Design	Placebo controlled, 14 days AI (75 or 225 mg) or placebo administered BID, 14 day follow up	Placebo controlled, 28 days TSI (open-label) followed by 28 days of AI/placebo 75 mg administered BID or TID, 56 days follow up	Placebo controlled, 28 days AI/placebo 75 mg administered TID, 14 days follow up	Open-label follow on, up to nine 28 day AI courses administered BID or TID
Primary endpoint	Change in FEV_1 (L)	Time to need for inhaled or IV anti-pseudomonal antibiotics	Change in respiratory symptoms as measured by CFQ-R respiratory symptoms domain	Safety (AEs, airway reactivity, vital signs, labs)
Major secondary endpoints	Change in PA density/susceptibility Sputum aztreonam concentrations	Change in pulmonary function Change in clinical symptoms by CFQ-R Physician/patient assessment of global change (GRCQ) Hospitalizations Change in weight Missed school/work days Change in CF symptoms/severity Change in PA density/susceptibility Disappearance/emergence of other pathogens	Change in pulmonary function Change in clinical symptoms by CFQ-R Hospitalizations Use of concomitant anti-pseudomonal antibiotics Change in CF symptoms/severity Missed school/work days Change in ability to produce sputum Change in PA density/susceptibility Disappearance/emergence of other pathogens	Change in pulmonary function Change in clinical symptoms by CFQ-R Hospitalizations Change in weight Missed school/work days Time to IV antibiotic use Change in PA density/susceptibility Disappearance/emergence of other pathogens
Key entry criteria	CF patients with PA ≥13 years No anti-pseudomonal or macrolide antibiotics 56 days prior to enrollment FEV1 ≥40% predicted	CF patients with PA ≥6 years ≥3 courses of TSI within the previous 12 months FEV1 ≥25% to ≤75% predicted	CF patients with PA ≥6 years No anti-pseudomonal or macrolide antibiotics within 28 days of study drug dosing FEV1 ≥25% to ≤75% predicted	Participated in CP-AI-005 or CP-AI-007 ≥6 years
Status	Complete	Complete	Complete	Ongoing, interim data reported

Common features between clinical trials included:

- Inclusion of patients with confirmed diagnoses of cystic fibrosis, including children (AI-003 ≥13 years, AI-005/007 ≥6 years)
- FEV_1 consistent with moderate to severe CF lung disease (AI-003 ≥40% predicted, AI-005/AI-007 FEV_1 25%-75% predicted)
- Double blind, with placebo control
- Block randomization (stratified by FEV_1 in AI-003, AI-007) with allocation from a central location
- Placebo: lactose diluted in saline, pH 4.2-7.5, osmolarity 200-400mOsmol/kg
- Use of specialized nebulizer device (eFlow Electronic Nebulizer)

Common exclusion criteria included:

- Oxygen saturation <90% or requirement for oxygen supplementation
- History of colonization with *B. cepacia*
- History of lung transplantation
- Recent acute change in chest x-ray
- Abnormal liver function (aspartate transaminase [AST]/alanine transaminase [ALT] >2 times upper limit of normal (ULN)(AI-003) or 5 x ULN (AI-005/007)
- Renal impairment (creatinine >1.5 x ULN (AI-003) or >2x ULN (AI-005/007)
- Pregnancy

Key differences between studies

- Prior use of antibiotics active against Pseudomonas spp was an exclusion criterion for AI-003, AI007; use of ≥3 courses of inhaled tobramycin within 12 months was an inclusion criterion for AI-005

- Use of prior or ongoing azithromycin was not an exclusion criteria in study AI-005, if part of a stable regimen at baseline
- Bronchodilators were used routinely prior to administration of aztreonam/placebo in studies AI-005 and -007; in study AI-003, bronchodilators were only continued if part of a prior treatment regimen
- Run-in period: All patients treated with inhaled tobramycin for 28 days prior to randomization (AI-005) had a 7-14 day screening period without treatment (AI-007)
- Dose: aztreonam lysine 75mg or 225mg bd (AI-003); 75mg bd or 75mg tds (AI-005) 75mg tds (AI-007)
- Duration: 14 days (AI-003), 28 days (AI-005/007)
- Primary endpoints: change in FEV_1in AI-003 at Day 14, time to need for anti-Pseudomonal antibiotics up to 56 days (AI-005), change in respiratory symptoms at 28 days, measured by the Respiratory Domain score in the Cystic Fibrosis Questionnaire (Revised)(CFQ-R) (AI-007)

The CFQ-R is a validated tool that assesses quality of life in various domains, with different versions used for patients of different ages. It encompasses three symptoms scales based on perception of respiratory symptoms, digestive symptoms and weight over the previous two weeks. For Phase 3 studies, the respiratory domain questions (4 for children, 6 for adults, each on a 4 point scale), normalized on a scale from 0 to 100 were used as endpoints following consultation with the US FDA. The minimal clinically important difference, based in studies where inhaled tobramycin was administered for stable disease and exacerbations, was defined as a difference in score of 5 points.

Study AI-003

Study AI-003 was a Phase 2 clinical trial that compared the efficacy and safety of inhaled aztreonam lysine 75mg bd and 225mg bd against placebo for 14 days at 21 centres in the United States. Of 131 patients screened for eligibility, 105 were randomized to receive placebo (n=32), aztreonam lysine 75mg bd (n=38) and aztreonam lysine 225mg bd (n=33). At baseline, higher proportions of patients had FEV_1<60% and a higher proportion of patients had colonization with non-susceptible Pseudomonas (aztreonam MIC >8μg/mL) in the aztreonam lysine 75mg group. Adherence to study medication was good in this short study.

On the primary outcome measure, change in FEV_1 at Day 14, there was no difference in FEV_1 at Day 14 compared to placebo between groups. There were no differences in other spirometric endpoints (forced vital capacity [FVC], forced expiratory flow between 25% and 75% of FVC [FEF_{25-75}]) between groups. There was a significant reduction in sputum PA concentration at Day 14 (-2.15 $\log_{10}$ colony forming units [CFU]/mL)(Table 12). In the 225mg bd group, there was a trend toward increased respiratory symptoms attributed to treatment and this dose was not investigated in later trials. There were no differences in other clinical outcomes (hospitalisations, antibiotic use in non-responders) in this small trial.

Table 12: Sputum Pseudomonas concentrations in Phase 2 study AI-003

Timepoint	Treatment as Randomized		
	Placebo (N = 32)	75 mg AI (N = 38)	225 mg AI (N = 35)
Day 0			
Mean	34,563,075.3	54,314,940.0	51,170,379.0
SD	61,204,930.4	131,589,262.2	115,548,269.8
Median	4,300,000.0	14,200,000.0	3,400,000.0
Minimum	0	40	2050
Maximum	246,000,000	736,000,000	456,000,000
n	30	35	30
Day 7			
Mean	80,143,962.8	6,198,417.6	4,122,437.2
SD	270,865,306.6	15,652,975.0	14,044,263.5
Median	5,400,000.0	283,000.0	10,000.0
Minimum	80	20	0
Maximum	1,468,000,000	84,000,000	73,254,000
n	29	34	29
Day 14			
Mean	101,604,617.2	14,430,843.5	4,455,064.1
SD	229,605,463.8	33,475,142.3	9,041,199.7
Median	3,200,000.0	175,000.0	88,000.0
Minimum	1056	20	0
Maximum	1,000,000,000	142,400,000	40,000,000
n	30	32	29

Source: Table 14.2.1.3.1.

Study AI-005

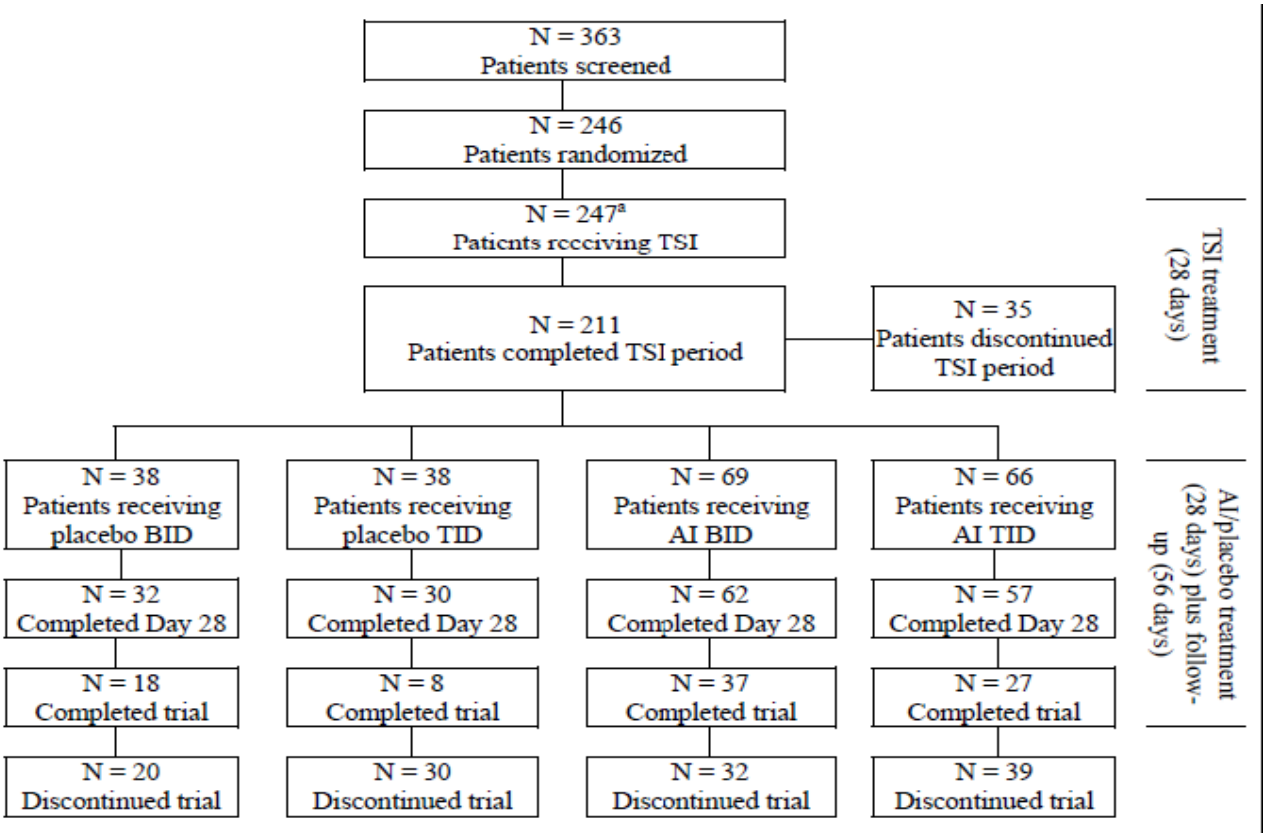
The Phase 3 study AI-005 evaluated the efficacy and safety of two dosing regimens of aztreonam lysine (75mg bd and 75mg tds) against placebo (bd and tds). Of the 246 patients enrolled and randomized, 211 patients completed the 28 day inhaled tobramycin course in the run-in period, and were allocated to received aztreonam lysine 75mg bd (n=69), 75mg tds (n=66), or placebo (bd, n=38; tds, n=38)(Figure 1). There were no significant differences in demographics, disease severity or carriage of non-susceptible PA at baseline. A high proportion of patients discontinued the trial upon meeting the primary endpoint (63%); most discontinuations occurred subsequent to the 28 day treatment period.

The median time to receipt of inhaled or intravenous antibiotics due to predefined symptoms was estimated to be 21 days longer in the groups that received aztreonam lysine than placebo (92 days vs 71 days, p=0.007)(Table 13). On Day 84, the Kaplan Maier estimate for treatment failure was 33% in the aztreonam groups. The proportions of patients that received antibiotics in the inhaled aztreonam groups was 28% and 36% for the bd and tds dosing groups respectively, and 32% and 68% in the bd and tds placebo groups respectively.

In secondary analyses, aztreonam lysine was associated with an improvement in the mean CFQ-R respiratory domain score compared to placebo at Day 28 (difference 5.0, p=0.02). There were also small improvements in FEV_1 change from baseline at Day 28 (6.3%,

p=0.001) and 14 days after completion of treatment (5.8%, p=0.003) compared to placebo. However, the mean change

Figure 1: Disposition of patients in Phase 3 study AI-005



associated with treatment was much smaller than the variation within treatment groups. Mean sputum concentration of Pseudomonas in the aztreonam lysine groups were lower than in placebo (difference 0.66 $\log_10$, p=0.006) at Day 28, but had returned to baseline levels by Day 42.

Table 13: Time to need for antibiotics due to pre-defined symptoms in study AI-005

Statistic	Treatment					
	Placebo			AI		
	BID (N = 38)	TID (N = 38)	Pooled (N = 76)	BID (N = 69)	TID (N = 66)	Pooled (N = 135)
Min	10	11	10	3	2	2
25th percentile	59	43	45	77	56	59
Median	-	54	71	-	87[b]	92[b]
95% CI for median	(71, -)	(46, 66)	(57, 97)	(89, -)	(71, -)	(89, -)
75th percentile	-	97	97	-	-	-
Max	71	97	97	92	87	92
Number of censored values	26	12	38	50	42	92
Number of events	12	26	38	19	24	43
p-value[a]				0.0019	0.1816	0.0070

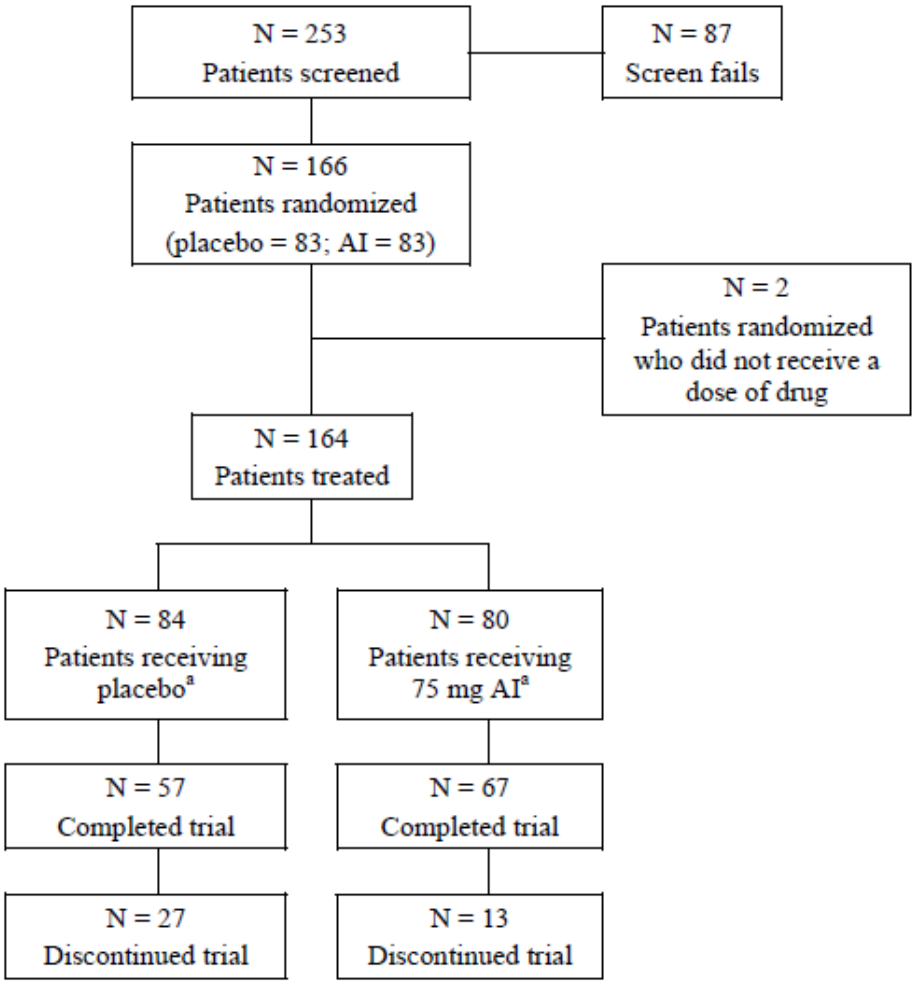
Source: Table 14.2.1.1.1.
- = not estimable.
[a] All comparisons are made against pooled placebo.
[b] Note that estimate is outside the nominal 84-day study period.

Study AI-007

The Phase 3 study AI-007 was a multicentre double blind clinical trial where patients with cystic fibrosis were allocated to receive either aztreonam lysine 75mg tds or placebo for 28 days. Of 253 patients screened for eligibility, 166 were enrolled and 164 received either aztreonam lysine (n=80) or placebo (n=84) (Figure 2). There were no significant differences in demographics, disease severity or carriage of non-susceptible PA at baseline. There were significant rates of discontinuation, mainly due to adverse events, in both aztreonam and placebo groups.

In the primary analysis, the mean change in the CFQ-R respiratory domain score from baseline at 28 days was +7.08 in the aztreonam group and -2.68 in the placebo group ($p<0.001$)(Table 14). This change was maintained 14 days following completion of treatment (aztreonam +0.62, placebo -5.71, $p=0.015$) (Table 14; Figure 3). A higher proportion of aztreonam patients reported an improvement in scores (aztreonam 56%, placebo 37%).

Figure 2: Patient disposition in study AI-007



Source: Tables 14.1.1.1 and 14.1.1.2.

[a] Patients who received at least part of one dose of trial drug. Patient 40954 was randomized to receive AI but received placebo. This patient is summarized in the placebo group.

In secondary analyses, there were improvements in FEV_1 change from baseline at Day 28 in patients treated with aztreonam (+7.9%) compared to placebo (-2.4%, $p<0.001$). Differences

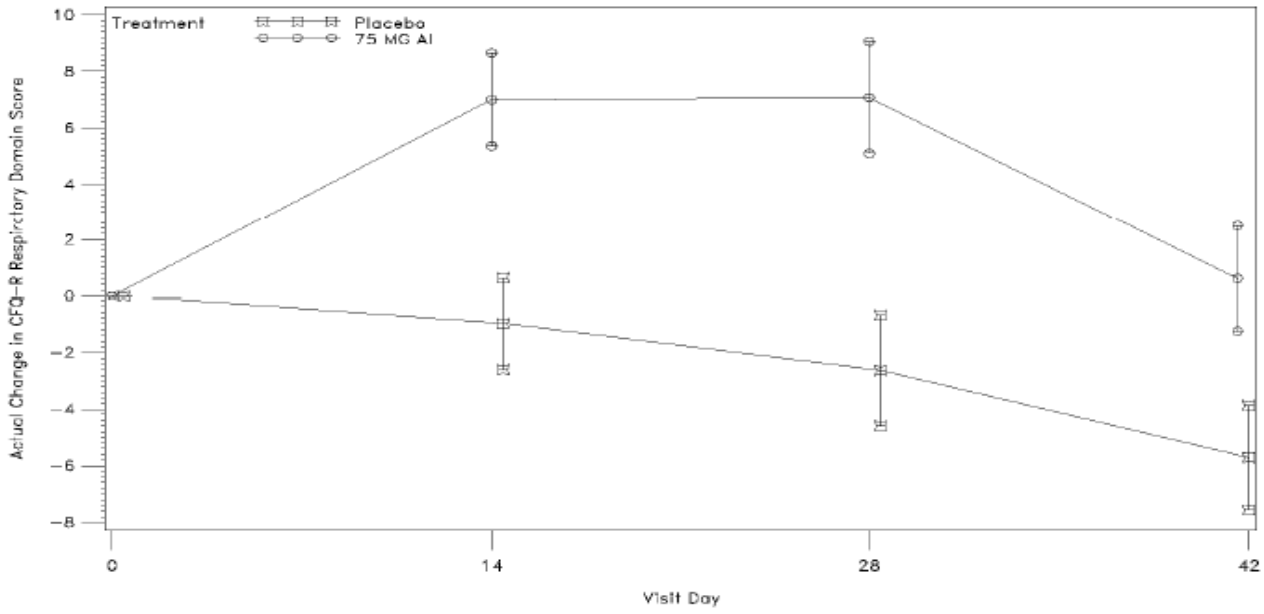
in FVC improvement (0.201 L) and FEV25-75 (0.16 L/sec) were consistent with changes in FEV_1. The sputum concentration of PA decreased by 1.5 log at Day 28 in the aztreonam group but had increased to baseline levels 14 days following completion of treatment.

Table 14: Change in CFQ-R respiratory domain scores from Day 0 in study AI-007

Timepoint	Treatment	
	Placebo (N = 84)	75 mg AI (N = 80)
Day 14		
Mean (± SD)	-0.27 (15.32)	7.78 (16.16)
n	83	80
Adjusted mean	-0.98	7.01
Treatment difference: 75 mg AI – placebo	7.98	
95% CI (p-value)	3.50, 12.47 (p = 0.0006)	
Day 28		
Mean (± SD)	-1.91 (18.64)	7.88 (18.88)
N	83	80
Adjusted mean	-2.63	7.08
Treatment difference: 75 mg AI – placebo	9.71	
95% CI (p-value)	4.31, 15.11 (p = 0.0005)	
Day 42		
Mean (± SD)	-5.09 (17.02)	1.32 (18.31)
N	83	80
Adjusted mean	-5.71	0.62
Treatment difference: 75 mg AI – placebo	6.33	
95% CI (p-value)	1.22, 11.43 (p = 0.0154)	

Source: Table 14.2.1.2.1.

Figure 3: Change in CFQ-R respiratory domain scores over time in study AI-007



Source: Table 14.2.1.2.1.
CFQ-R respiratory domain scores range from 0 to 100.

Use of antipseudomonal antibiotics other than aztreonam was higher in the placebo group (36%) compared to the aztreonam group (17%, p=0.01), and there was a trend to a lower proportion hospitalized in the aztreonam group (5.0%) compared to placebo-treated patients (14.3%, p=0.064).

An integrated analysis across both Phase 3 studies was performed. At baseline, there were no significant differences in demographics or disease severity between placebo groups and aztreonam groups. The change in CFQ-R respiratory domain scores and the proportion reporting improvement at Day 28 were greater in study AI-007 than study AI-005 (Table 15). Similarly, improvement in FEV_1, fall in sputum Pseudomonas concentrations and the proportion of patients not using antipseudomonal antibiotics associated with inhaled aztreonam were greater in study AI-007 than study AI-005. Changes in FEV_1 and sputum *Pseudomonas* concentrations were similar to that reported after clinical trials of inhaled colistin and tobramycin.

Time to need for antibiotics was prolonged in the group that received aztreonam lysine in AI-005 and not estimable in study AI-007. Only small numbers of study subjects were hospitalized; there were no significant differences between placebo and inhaled aztreonam groups. There was a small mean weight gain (0.19-0.61kg) in the groups that received aztreonam in the Phase 3 studies, and no change in mean weight in the placebo groups.

There was a greater difference in Day 28 CFQ-R respiratory domain scores and FEV_1 between placebo and aztreonam groups in patients with baseline FEV_1<50% of predicted. Similar differences were observed in Day 28 CFQ-R respiratory domain scores and FEV_1 between placebo and aztreonam groups in patients with PA isolates with aztreonam MIC >8µg/mL. Differences in Day 28 CFQ-R respiratory domain scores were greater in female patients than male patients, but these differences were not seen in FEV_1. There were insufficient numbers of patients <12 years of age to meaningfully compare response by age.

Table 15: Categorical change in CFQ-R respiratory domain score in studies AI-005 and AI-007

	CP-AI-005				CP-AI-007	
	Placebo Pooled (N = 76) n (%)	AI BID (N = 69) n (%)	AI TID (N = 66) n (%)	AI Pooled (N = 135) n (%)	Placebo TID (N = 84) n (%)	AI TID (N = 80) n (%)
Day 14						
n	73	67	65	132	83	80
Improved	24 (32.9)	36 (53.7)	32 (49.2)	68 (51.5)	34 (41.0)	46 (57.5)
Stable or no change	23 (31.5)	12 (17.9)	14 (21.5)	26 (19.7)	15 (18.1)	15 (18.8)
Worsened	26 (35.6)	19 (28.4)	19 (29.2)	38 (28.8)	34 (41.0)	19 (23.8)
p-value[d]	-	0.0369	0.0923	0.0273	NA	NA
Day 28						
n	73	67	65	132	83	80
Improved	27 (37.0)	37 (55.2)	31 (47.7)	68 (51.5)	31 (37.3)	45 (56.3)
Stable or no change	18 (24.7)	12 (17.9)	15 (23.1)	27 (20.5)	15 (18.1)	15 (18.8)
Worsened	28 (38.4)	18 (26.9)	19 (29.2)	37 (28.0)	37 (44.6)	20 (25.0)
p-value		0.0299	0.1405	0.0289	0.0055	
Day 42						
n	-	-	-	-	83	80
Improved	-	-	-	-	25 (30.1)	36 (45.0)
Stable or no change	-	-	-	-	15 (18.1)	15 (18.8)
Worsened	-	-	-	-	43 (51.8)	29 (36.3)

Source: CP-AI-005 CSR Table 14.2.2.23.1 and CP-AI-007 CSR Table 14.2.1.5.1

Improved – increase in score of ≥ 5

Stable or no change – change of less than 5 (increase or decrease)

Worsened – decrease in score of ≥ 5

NA – not analyzed

p-values from Cochran-Mantel-Haenszel test stratified by categorized baseline response (and baseline disease severity stratum for CP-AI-007). All comparisons are made against the placebo group within each study.

Note: CFQ-R was collected at Day 42 in CP-AI-007 only

Study AI-006

In the open label roll-over study AI-006, patients were administered up to nine 28-day courses of inhaled aztreonam lysine, each course followed by a 28-day period off aztreonam. Patients were not withdrawn if they received antipseudomonal antibiotics other than aztreonam. There was a pattern of improvement in FEV_1 following treatment, followed by deterioration while not on inhaled aztreonam (Figure 4). A similar pattern was described in CFQ-R respiratory domain scores related to treatment. Improvements in CFQ-R respiratory domain scores on treatment were more pronounced in patients receiving tds dosing of inhaled aztreonam (Table 16). No trends in pre-treatment FEV_1 or CFQ-R respiratory domain scores were evident at the end of the first 3 courses of treatment (Tables 16, 17). Changes in PA concentrations varied with treatment; the mean variation in sputum bacterial concentrations was less than 1 log, although there was a wide variation in response.

The proportion of patients hospitalized was similar in the inhaled aztreonam bd and tds groups in study AI-006. The mean change in body weight was greater following the third course of inhaled aztreonam than after the first two courses of inhaled aztreonam. The proportion of patients not responding, according to symptoms, FEV_1 and bacterial

concentration criteria, were lower in patients receiving inhaled aztreonam, and similar in patients receiving bd and tds dosing.

Figure 4: Percentage change in FEV_1 on and off treatment in study AI-006

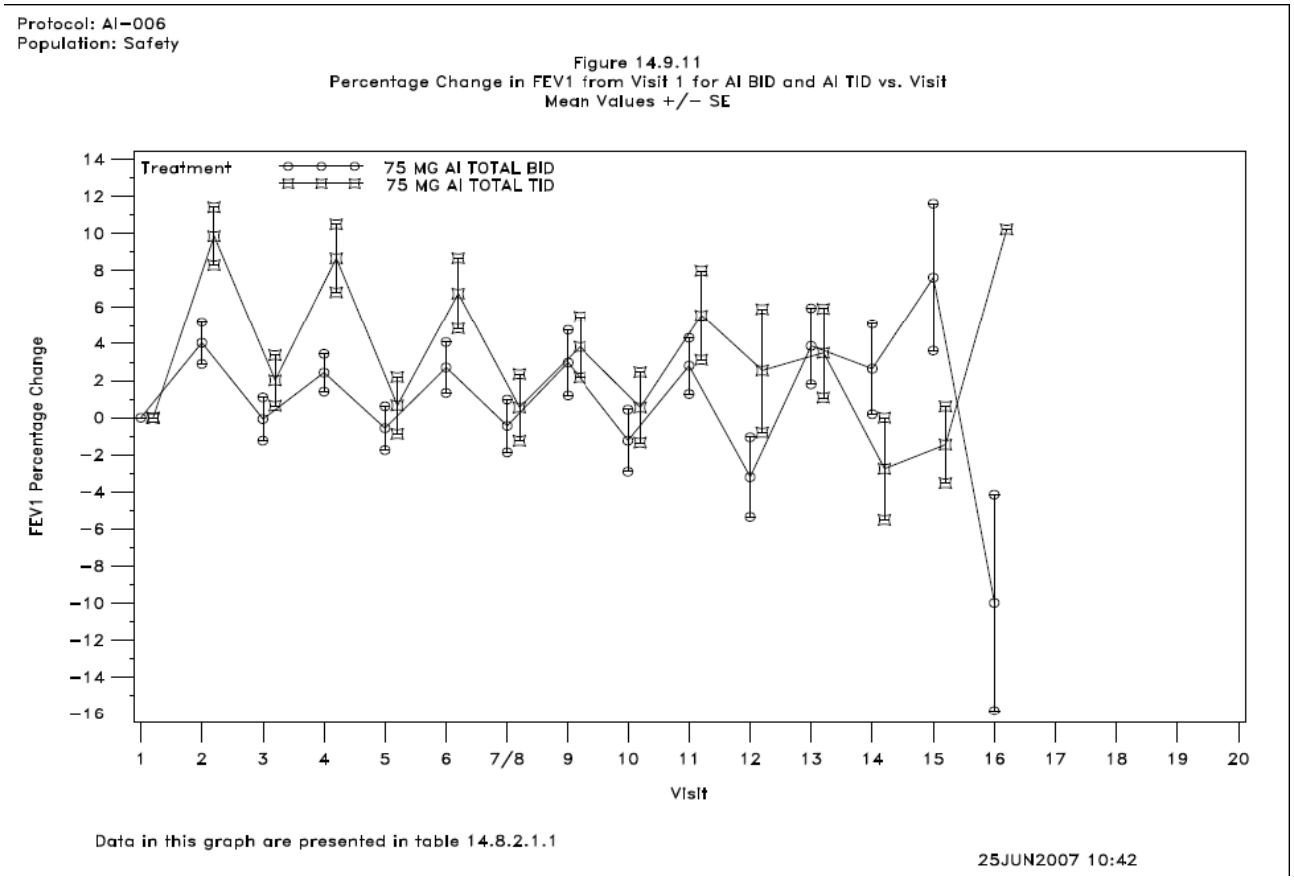


Table 16: Change in CFQ-R respiratory domain scores from Day 0 in open label study AI-006

	CP-AI-005			CP-AI-007
	AI BID (N = 82)	**AI TID (N = 74)**	**AI Pooled (N = 156)**	**AI TID (N = 51)**
End Course 1 (Day 28)				
n	78	73	151	51
Mean (SD)	3.53 (12.53)	7.61 (15.78)	5.50 (14.29)	6.26 (17.26)
Median	5.56	5.56	5.56	5.56
Range	-38.89 - 27.78	-33.33 - 66.67	-38.89 - 66.67	-38.89 - 72.22
End Course 2 (Day 84)				
n	75	67	142	39
Mean (SD)	2.93 (13.98)	4.39 (16.00)	3.62 (14.93)	9.83 (16.88)
Median	0.00	5.56	0.00	11.11
Range	-50.00 - 33.33	-38.89 - 55.56	-50.00 - 55.56	-33.33 - 55.56
End Course 3 (Day 140)				
n	70	59	129	29
Mean (SD)	0.08 (19.74)	6.36 (20.56)	2.95 (20.28)	9.67 (15.48)
Median	0.00	0.00	0.00	5.56
Range	-61.11 - 33.33	-44.44 - 50.00	-61.11 - 50.00	-22.22 - 50.00

Source: SCE Tables 2.4.4.2 and 2.4.4.3

Table 17: Percentage change in FEV_1 in open label study AI-006

	AI BID (N = 82)	AI TID (N = 125)
End Course 1 (Day 28)		
n	80	122
Mean (SD)	4.05 (10.27)	9.86 (17.27)
Median	3.71	6.99
Range	-17.50 - 33.33	-25.13 - 108.74
End Course 2 (Day 84)		
n	75	107
Mean (SD)	2.43 (8.85)	8.66 (18.98)
Median	3.50	5.85
Range	-16.86 - 23.68	-44.16 - 110.16
End Course 3 (Day 140)		
n	70	90
Mean (SD)	2.72 (11.51)	6.76 (18.22)
Median	3.59	4.41
Range	-31.74 - 28.37	-37.57 - 93.20

Source: CP-AI-006 CSR Table 14.8.2.1.1

Bacterial resistance

In vitro studies suggest that aztreonam is active against a broad range of gram negative bacilli, including PA and some strains of *Burkholderia cepacia*. Studies have reported MIC_{50} of ≤2µg/mL and MIC_{90} of 32-64 µg/mL for gram negatives generally, and MIC_{50} of 4-8µg/mL and MIC_{90} from 16-64µg/mL for *Pseudomonas* specifically, with 63-74% of *Pseudomonas* reported susceptible to aztreonam. Criteria listed in the NCCLS 2004 guidelines define isolates with an MIC≤8µg/mL as susceptible and isolates with an MIC≥32µg/mL as resistant for gram negative bacilli.

The mean change in sputum *Pseudomonas* concentrations at Day 28 was higher where baseline aztreonam MIC was≤8µg/mL, but this difference was not statistically significant. The proportion of patients where new pathogens were isolated during or after treatment was assessed. There were no significant differences in the proportion of patients that acquired *Staphylococcus aureus* (9.1% vs 8.0%), *Stenotrophomonas maltophila* (3.7% vs 1.5%) or *Alcaligenes xylosoxidans* (1.1% vs 3.6%) at Day 28 compared to placebo. *Burkholderia cepacia* was isolated from two patients prior to treatment, was not isolated following treatment in any patient in Phase 3 studies and was newly isolated intermittently in three patients in the rollover study AI-006.

Summary of efficacy

Phase 2 and 3 studies were conducted in patients >6 years of age with cystic fibrosis with evidence of airway colonization with *Pseudomonas aeruginosa*, with no evidence of active infection.

Clinical trials evaluated 14 to 28 day courses of inhaled aztreonam lysine either twice or three times/day.

Outcome measures included subjective (CFQ-R respiratory domain scores) and objective (sputum Pseudomonas concentrations, FEV_1) at the end of treatment, compared to baseline.

A high proportion of patients withdrew from the trials, most due to unrelated adverse events during and after the treatment course with inhaled aztreonam.

There were greater improvements in symptoms and FEV_1 from baseline in patients treated with inhaled aztreonam compared to placebo at 28 days. Changes in FEV_1 on treatment were moderate (median +50mL to +150mL) and there was a wide variation in response.

Repeat courses were associated with improvement in outcome measures, with deterioration off treatment; there was no long term change in baseline pre-treatment measures in the open label follow up study AI-006.

A high proportion of patients in the placebo arm had improvement in CFQ-R (37%) and there was a wide variation in the change in FEV_1 from baseline.

Studies had limited power to examine other clinical endpoints, such as hospitalizations or the need for intravenous antibiotics.

Acquired bacterial resistance and colonization with resistant organisms was not demonstrated over short durations of follow up.

Safety

The majority of patients in both the inhaled aztreonam and placebo groups reported adverse events, consistent with underlying cystic fibrosis-related lung disease. Adverse events that were reported more frequently in aztreonam groups than placebo included cough, nasal congestion, fever and wheezing. Other significant adverse events included bronchospasm and rash, but both occurred in a similar proportion of the placebo group.

Data were available on 41 subjects that received≤3 doses of inhaled aztreonam lysine in Phase 1 studies, and 289 subjects in Phase 2/3 studies that received 14-28 days of inhaled aztreonam lysine (Table 18). A number of patients participated in multiple studies. Data were also presented on subjects in the roll-over study AI-006 (n=207) that received up to nine additional 28-day courses of inhaled aztreonam.

Table 18: Exposure in placebo controlled Phase 2/3 studies AI-003, AI-005 and AI-007

Duration of Treatment (Days)[b]	AI		
	75 mg BID (N = 106) n (%)	225 mg BID (N = 37) n (%)	75 mg TID (N = 146) n (%)
1 ≤ duration < 7	1 (0.9)	0	3 (2.1)
7 ≤ duration < 14	1 (0.9)	3 (8.1)	4 (2.7)
14 ≤ duration < 21	36 (34.0)	34 (91.9)	4 (2.7)
21 ≤ duration < 28	13 (12.3)	0[b]	17 (11.6)
28 ≤ duration < 35	55 (51.9)	0[b]	116 (79.5)
35 ≤ duration < 42	0	0[b]	1 (0.7)
42 ≤ duration < 56	0	0[b]	1 (0.7)

Source: SCS Table 4.1.1.

[a] The 75 mg BID group includes patients from Studies CP-AI-003 and -005, the 225 mg BID group includes patients from Study CP-AI-003, and the 75 mg TID group includes patients from Studies CP-AI-005 and -007. See Table 2 for additional details. Planned treatment duration was 14 days for CP-AI-003 and 28 days for CP-AI-005 and -007.

[b] Within each study, duration of exposure is the number of days from first to last dose. Patients may not have received treatment as planned for all days indicated; therapy may have been interrupted.

Surveillance plan

A priori concerns included the possibility of allergic phenomena (including rash) and respiratory tolerability. Prior evidence suggests that despite the structural similarities between aztreonam (a monobactam) and the beta-lactams, cross reactions are uncommon in patients with a history of beta-lactam allergy. Although systemic absorption was low compared to the concentrations achieved after intravenous dosing, and the safety of systemic dosing has been established previously, surveillance for organ dysfunction was performed. Assessments of adverse events were graded according to the Common Toxicity Criteria.[4] Blood and sputum samples were taken at scheduled clinic visits. Blood tests included a full blood examination, urea, creatinine and electrolytes, liver function testing. FEV_1 was assessed prior to and 30 minutes after treatment. Sputum was cultured from *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia cepacia*, *Stenotrophomonas maltophila* and *Alcaligenes (Achromobacter) xylosoxidans.*

Safety in Phase 1 studies

In the Phase 1 study AI-001 in healthy subjects there were no serious adverse events reported. Cough resulted in the cessation of study drug in one patient, and other drug-related adverse events included headache, dizziness and complaints of unpleasant taste. In the Phase 1 study AI-002 in subjects with cystic fibrosis, patients received increasing doses of inhaled

[4] **Common Toxicity Criteria** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

aztreonam. No serious adverse events were noted. One patient was withdrawn from the study after the first 75mg dose after an asymptomatic decrease in 20% FEV_1 after administration of 150mg aztreonam was noted. Moderate adverse events included chest pain, cough and headache in 1 patient each.

Safety in Phase 2/3 studies

Commonly reported adverse events that were reported in a higher proportion of patients that received inhaled aztreonam than placebo included cough (58% vs 51%), nasal congestion (18% vs 12%), wheezing (15% vs 10%), throat pain (13% vs 11%), fever (12% vs 6%), chest discomfort (9% vs 6%), rhinorrhoea (8% vs 6%), abdominal pain (7% vs 5%) and vomiting (6% vs 4%) (Table 19). Haemoptsis was reported in a lower proportion of subjects in the aztreonam groups compared to placebo (9.8% vs 12%). There were no significant differences in the proportions reporting common adverse events while on treatment.

Table 19: Common adverse events (>5%) in studies AI-005 and AI-007

Event (Preferred Term)[a]	Placebo Pooled (N = 160) n (%)	AI		
		75 mg BID (N = 69) n (%)	75 mg TID (N = 146) n (%)	Pooled (N = 215) n (%)
Abdominal pain	8 (5.0)	6 (8.7)	10 (6.8)	16 (7.4)
Chest discomfort	10 (6.3)	9 (13.0)	11 (7.5)	20 (9.3)
Cough	82 (51.3)	45 (65.2)	79 (54.1)	124 (57.7)
Nasal congestion	19 (11.9)	16 (23.2)	23 (15.8)	39 (18.1)
Pharyngolaryngeal pain	17 (10.6)	10 (14.5)	18 (12.3)	28 (13.0)
Pyrexia	9 (5.6)	6 (8.7)	19 (13.0)	25 (11.6)[c]
Rhinorrhoea	10 (6.3)	7 (10.1)	10 (6.8)	17 (7.9)
Vomiting	7 (4.4)	3 (4.3)	9 (6.2)	12 (5.6)
Wheezing	16 (10.0)	9 (13.0)	23 (15.8)	32 (14.9)

Source: SCS Table 6.3.2.

[a] More frequent events are defined as those with incidence ≥ 1% higher in the pooled AI group (compared with placebo).

[b] The placebo and 75 mg TID groups include patients from both studies; the 75 mg BID group includes patients from Study CP-AI-005. See Table 2 for additional details. Planned study durations in days (treatment + follow-up): CP-AI-005 (28 + 56), CP-AI-007 (28 + 14).

[c] p = 0.0474 (Fisher's exact test).

Drug related adverse events that were reported in a higher proportion of patients in the inhaled aztreonam group included cough (16% vs 10%), chest discomfort (4% vs 1%), hoarseness (1% vs 0%) and disturbances of taste (2% vs 0%) (Table 20). Only a minority of most common adverse events were attributed to the study drug, including fever (1% vs 1%) (Table 20). Severe drug-related adverse events were reported in 3 patients on placebo (2%) and 5 patients in the inhaled aztreonam group (3%). Severe drug related adverse events attributed to the study drug in the inhaled aztreonam group included decreased appetite, exertional dyspnoea, cough and diarrhoea. Similar proportions of patients reported adverse events of severe intensity in Phase 2/3 studies. These included cough (aztreonam 7%, placebo 8%), dyspnoea (2.1% vs 2.6%) nasal congestion (1.7% vs 0%), impaired pulmonary function test results (2.1% vs 0.5%) and arthralgia (1% vs 0%).

Table 20: Adverse events related to study drug in Phase 2/3 studies AI-003, AI-005 and AI-007.

System Organ Class Preferred Term	Placebo Pooled (N = 191) n (%)	AI			
		75 mg BID (N = 106) n (%)	225 mg BID (N = 37) n (%)	75 mg TID (N = 146) n (%)	Pooled (N = 289) n (%)
Any drug-related AE[b]	48 (25.1)	28 (26.4)	14 (37.8)	48 (32.9)	90 (31.1)
Respiratory, thoracic and mediastinal disorders					
Chest discomfort	2 (1.0)	2 (1.9)	2 (5.4)	4 (2.7)	8 (2.8)
Cough	19 (9.9)	14 (13.2)	7 (18.9)	24 (16.4)	45 (15.6)
Crackles lung	3 (1.6)	1 (0.9)	1 (2.7)	2 (1.4)	4 (1.4)
Dysphonia	3 (1.6)	1 (0.9)	0	2 (1.4)	3 (1.0)
Dyspnoea	4 (2.1)	1 (0.9)	2 (5.4)	3 (2.1)	6 (2.1)
Haemoptysis	4 (2.1)	0	1 (2.7)	2 (1.4)	3 (1.0)
Hoarseness	0	2 (1.9)	1 (2.7)	0	3 (1.0)
Nasal congestion	1 (0.5)	1 (0.9)	1 (2.7)	2 (1.4)	4 (1.4)
Pharyngolaryngeal pain	5 (2.6)	2 (1.9)	1 (2.7)	3 (2.1)	6 (2.1)
Productive cough	13 (6.8)	0	2 (5.4)	3 (2.1)	5 (1.7)
Throat irritation	3 (1.6)	1 (0.9)	0	3 (2.1)	4 (1.4)
Wheezing	6 (3.1)	3 (2.8)	3 (8.1)	4 (2.7)	10 (3.5)
Gastrointestinal disorders					
Dysgeusia	0	1 (0.9)	4 (10.8)	0	5 (1.7)
Vomiting	2 (1.0)	1 (0.9)	0	2 (1.4)	3 (1.0)
Nervous system disorders					
Headache	1 (0.5)	1 (0.9)	2 (5.4)	3 (2.1)	6 (2.1)
General disorders and administration site conditions					
Chest discomfort	0	2 (1.9)	1 (2.7)	0	3 (1.0)
Pyrexia	2 (1.0)	2 (1.9)	1 (2.7)	0	3 (1.0)

Source: SCS Table 6.6.2.1.

[a] The placebo group includes patients from all three studies, the 75 mg BID group includes patients from Studies CP-AI-003 and -005, the 225 mg BID group includes patients from Study CP-AI-003, and the 75 mg TID group includes patients from Studies CP-AI-005 and -007. See Table 2 for additional details. Planned study durations in days (treatment + follow-up): CP-AI-003 (14 + 14), CP-AI-005 (28 + 56), CP-AI-007 (28 + 14). Patients who were treated in multiple studies are included multiple times.

[b] Drug-related AEs are those judged by the investigator to have a causality of possible or probable.

Serious adverse events

In Phase 2/3 studies, 38 patients had serious adverse events that were regarded as life-threatening or resulted in hospitalization or significant disability. The majority of serious adverse events reflected underlying cystic fibrosis, including pulmonary exacerbations (n=27) and bowel obstruction (n=3). Serious adverse events that were noted in a greater proportion in the aztreonam group included chest discomfort (1% vs 0%) and impaired pulmonary function tests (2% vs 1%). Similar proportions of patients in both groups reported cough (3%), haemoptsis (1%), fever (1%) and wheezing (1% vs 0%) as serious adverse events. Serious adverse events that were considered related or possibly related to study drug that received inhaled aztreonam (n=4) included rash, cough, arthralgia and dyspnoea.

In the rollover study AI-006, higher proportions of patients reported serious adverse events than in placebo-controlled studies, reflecting the longer duration of follow up. In particular, cough (2% placebo controlled studies, 20% open label study), fatigue (0% vs 4%), haemoptsis (1% vs 4%), impaired pulmonary function tests (2% vs 8%) and fever (1% vs 4%) were reported in a higher proportion of patients in the open label study. After adjusting for the duration of exposure, rates of serious adverse events were similar in the inhaled aztreonam group in placebo controlled studies AI-005 and AI-007 to the open label study AI-006.

Adverse events leading to discontinuation

The proportion of patients who discontinued the study drug due to adverse events was higher in the placebo group in study AI-005 (aztreonam bd 39%, aztreonam tds 55%, placebo 62%) and study AI-007 (14% aztreonam vs 27% placebo). In all Phase 2/3 studies, 11 patients had discontinued treatment due to intolerance of study drug; of the 9 subjects that received aztreonam, reported adverse events included rash, headache, impaired FEV_1, tinnitus, post-dose chest tightness, fatigue and dyspnoea, cough, arthralgia and haemoptsis and dyspnoea.

Pulmonary tolerability

Study AI-005 incorporated a 28-day run-in inhaled tobramycin Phase, and an inclusion criterion was the use of ≥3 courses of inhaled tobramycin within 12 months. Subjects in both Phase 3 studies were administered a short acting bronchodilator prior to administration of study drug. FEV_1 was measured prior to study drug administration and 30 minutes following study drug administration on the first dose, at Day 7, 14 and 28. The proportion of subjects with an acute ≥15% decline in FEV_1 was low and similar between placebo (3.2% after first dose) and the inhaled aztreonam groups (2.1%). There were no significant differences in the proportion reporting a ≥15% decline in FEV_1 at later endpoints or in the rollover study AI-006. Severe adverse events related to the respiratory tract reported in greater proportions in patients receiving inhaled aztreonam than placebo included chest discomfort (1.4% vs 0%), nasal congestion (2.3% vs 0%) and productive cough (4.7% vs 3.7%). Severe cough (9.3% vs 9.4%), dyspnoea (2.8% vs 3.1%), haemoptsis (0.5% vs 0.6%) and respiratory tract congestion (1.4% vs 1.9%) were seen at similar rates in the inhaled aztreonam and placebo groups.

Fever

More patients in the inhaled aztreonam groups reported pyrexia as an adverse event than those in the placebo groups (12% vs 6%, p=0.047) in the Phase 3 studies AI-005 and AI-007. In all but two patients receiving inhaled aztreonam, fever was not felt to be related to the study drug. In study AI-006, the incidences of fever during the first, second and third treatment courses were 4%, 4% and 7% respectively. No dose response relationship was evident between patients on the bd and tds regimens. Fever was not reported as a severe adverse event in patients receiving inhaled aztreonam in Phase 2/3 studies. Fever was reported as a serious adverse event in two patients receiving inhaled aztreonam in placebo controlled studies, and 9 patients in the rollover study AI-006.

Fever was more common in female patients receiving aztreonam (14% vs male/aztreonam 9%), and more common in paediatric patients 13% vs 8% in adults). 25% of patients aged 6-12 years, and 16% of patients aged 12-18 years that received aztreonam reported fever, compared to no paediatric patients that received placebo. There was no apparent association with patients who had a history of pre-existing allergy to beta-lactam antibiotics, and there were no associated symptoms suggestive of an allergic response. Of the 14 paediatric patients that reported fever in Phase 2/3 studies, 6 patients participated in the rollover study AI-006; one of these six patients reported fever during the rollover study. The cause of fever in paediatric patients was not clear. The sponsor suggests that fever may represent a reaction to endotoxin release related to bacterial killing (analogous to a Jarisch-Herxheimer reaction), but no data was presented to support this. The lack of association with wheezing, rash or beta-lactam allergy suggests that fever may not be an allergic reaction.

Rash

A rash was reported in 2% in both the inhaled aztreonam and placebo groups in Phase 2/3 studies. No severe rash was reported in Phase 2/3 studies or in the rollover study AI-006. Rash was only reported as a serious adverse event in one patient in the rollover study AI-006.

Allergic phenomena

As noted above, the incidence of bronchospasm or rash was low and not significantly different between placebo and inhaled aztreonam groups. No severe allergic reactions were reported in any patients treated with inhaled aztreonam in all studies. Three patients discontinued inhaled aztreonam due to possible allergic reactions. One patient with a pre-existing beta-lactam allergy reported a diffuse facial rash together with chest discomfort and throat tightness during a second course in inhaled aztreonam. A second patient had arthralgia and joint swelling three weeks after commencing inhaled aztreonam that was felt to be possibly related to the study drug. A third patient reported urticaria, rash and dizziness 3 days after commencing inhaled aztreonam that was felt to be possibly related to treatment.

A pre-existing allergy to beta-lactams was reported in 18% (n=87) of subjects in Phase 2/3 placebo controlled studies, and 26% (n=53) of subjects in the open label study AI-006. Many adverse events were more common in patients with a pre- existing allergy to beta-lactams in Phase 2/3 placebo controlled studies, including chest discomfort (13% vs 9%), cough (69% vs 48%), haemoptsis (17% vs 6%), fever (21% vs 9%) and rash (6% vs 1%) but the majority of adverse events were not felt related to the study drug.

Laboratory monitoring

In trials of intravenous aztreonam, reported adverse laboratory test result changes included increases in serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP).

For inhaled aztreonam, there were no significant differences in the proportion of patients reporting a shift to high or low white cell counts between placebo and aztreonam groups at the end of treatment, except that a higher proportion of patients reported a high eosinophil count in the aztreonam group compared to placebo (3.2% vs 1.7%). There were no significant differences in red cell parameters or platelet count associated with aztreonam at the end of treatment. No abnormal haematology results reported as adverse events were considered severe, and none were felt to be related to the study drug.

There were no significant differences in the proportion of patients in the placebo group and aztreonam groups reporting a shift to a high bilirubin, AST or ALT level at the end of treatment. A higher proportion of patients in the aztreonam group had a shift to a high gamma glutamyl transferase compared to placebo (4.0% vs 2.2%). A high proportion of patients in both aztreonam and placebo groups reported a shift to a high serum glucose at the end of treatment (15.2% vs 16.6%). There were no significant differences in serum sodium, potassium, creatinine or urea at the end of treatment between inhaled aztreonam and placebo groups. The majority of adverse events relating to serum chemistry parameters related to blood glucose or hepatic enzymes. The only severe adverse event reported in patients in the inhaled aztreonam group was a report of altered conscious state related to hyponatraemia. One patient discontinued inhaled aztreonam after an adverse event related to a moderately elevated blood glucose. One patient in study AI-006 had severe acute hepatitis that was not considered to be related to study drug; the hepatitis resolved over 4 days.

Deaths

No patients died in the placebo controlled studies, but one patient in study AI-006 died following the interim data cut-off. This patient was a 44 year old female with cystic fibrosis, with a prior history of haemoptsis (including embolization procedures), asthma, and CF-

related malabsorption and diabetes. Her FEV_1 was 36% of predicted at baseline. She received 28 days of inhaled aztreonam in study AI-005 and had a further seven courses of inhaled aztreonam in study AI-006. Multiple episodes of haemoptsis were reported that were not ascribed to the study drug. Episodes of haemoptsis during the third course, following the fourth course (requiring intubation) and following the fifth course were treated with embolization procedures. The patient died following the eighth course of inhaled aztreonam due to massive haemoptsis and cardiac arrest. Serial testing of *Pseudomonas aeruginosa* isolates from the patient suggested a trend to increasing MIC on treatment from 16μg/mL to 256-512 μg/mL.

Other special populations

Gender

A higher proportion of female patients in the inhaled aztreonam groups reported adverse events compared to male patients. Specific adverse events reported in a greater proportion of female patients in the inhaled aztreonam group included cough (59%, vs female/placebo 46%; male/aztreonam 46%), dyspnoea (13%, vs female/placebo 10%; male/aztreonam 6.1%), rhinorrhoea (14% vs female/placebo 7%; male aztreonam 4%), wheezing (18% vs female/placebo 8%; male/aztreonam 10%) and fever (14% vs female/placebo 8%, male/aztreonam 8.5%).

Age

There were a high proportion of patients reporting adverse events in adults ≥18 years of age, consistent with increased disease severity. Cough and fever were reported in a higher proportion of paediatric patients; cough was more common in aztreonam treated patients than placebo (12 (60%) vs 2 (40%)), and fever was reported in 28 (18%) of aztreonam-treated patients compared to no placebo-treated patients.

Drug-drug interactions

No formal drug interaction studies were performed. Analyses were presented to evaluate the potential effects of concomitant bronchodilators, dornase alfa, pancreatic enzymes, oral/inhaled steroids, azithromycin and tobramycin. Because these analyses are post hoc, they are potentially confounded by symptoms that prompted their use, particularly symptoms of exacerbations.

Summary of safety

Inhaled aztreonam seems to be well tolerated, with most adverse events attributable to underlying pulmonary disease.

In preclinical studies, local irritation (including squamous cell metaplasia) was observed at high level dosing in animals. Prior clinical experience with systemic aztreonam suggests that it is well tolerated.

The surveillance plan included monitoring for clinical and laboratory abnormalities. Other *a priori* concerns addressed by the surveillance plan included airway reactivity and allergic phenomena.

Studies were relatively small (Phase 2/3 studies n=289) and of relatively short duration (14-28 days). Further data was presented on patients that received up to 8 additional 28-day courses in an open label rollover study AI-006.

Common adverse events reported in a greater proportion of patients that received inhaled aztreonam included cough, nasal congestion and wheezing, but these were also reported in a high proportion of patients that received placebo.

Significant but uncommonly reported adverse events included rash and allergic phenomena. Fever was reported in a significant proportion of paediatric patients; the cause for this was not clear, although the lack of association with beta-lactam allergies and other symptoms suggest that this was not a manifestation of allergic phenomena.

There was one death in the open label rollover study; the sponsor's narrative suggests this was due to underlying disease.

No formal drug-drug interaction studies were performed. A post hoc analysis of adverse events stratified by use of concurrent medications was presented, but is confounded by the indication for use of concurrent medication.

Supplementary Clinical Evaluation

Gilead Sciences Pty Ltd submitted four volumes of supplementary data for Study CP-AI-006 in support of long-term efficacy and safety of multiple courses of aztreonam lysinate for inhalation.

The sponsor also provided an update on the Committee for Medicinal Products for Human Use (CHMP) review of the Cayston Marketing Authorisation Application in Europe. On 25 June 2009, the CHMP adopted a positive opinion for Cayston for the suppressive therapy of chronic pulmonary infections in adults with cystic fibrosis. This opinion is for conditional approval, contingent on the successful completion of an ongoing study and it reversed a negative opinion previously issued in March. As noted in Section 1.2, the EU application has now been approved.

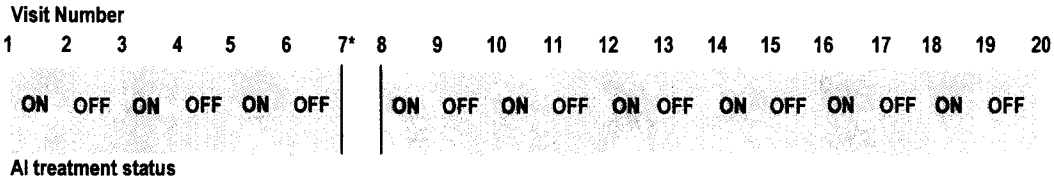
Study CP-AI-006

Study CP-AI-006 was a Phase 3, open-label, follow-on study of multiple courses of aztreonam lysinate for inhalation in cystic fibrosis patients. Patients were enrolled in 71 sites in the United States, Canada, Australia and New Zealand. The study was conducted from August 2005 to January 2009. Participants were male and female cystic fibrosis patients aged ≥ 6 years who had complied with Studies CP-AI-005 or CP-AI-007.

The primary objective was to evaluate the safety of repeated exposure to aztreonam for inhalation solution (AI). Secondary objectives included evaluation of the effects of repeated exposure to AI in disease-related endpoints and of microbiology.

Treatment was self-administered for up to nine 28 day courses of 75 mg aztreonam lysine and was administered either twice daily or three times daily as a continuation of the regimen in preceding Studies CP-AI-005 and CP-AI-007. Each course of treatment was separated by a 28 day off-treatment period. AI was administered using the eFlow electronic nebuliser. The study design is summarised in Figure 5: below

Figure 5: CP-AI-006 Study Design



*Visit 7 occurred only for patients enrolled under Protocol Versions 2 or 3 who discontinued the study early or who completed the first three courses of AZLI treatment (i.e., completed the study) before Protocol Version 4 was implemented (See Section 9.1.2). All other patients skip Visit 7 and continue to Visit 8. Patients who attend for Visit 7 and continue in the study also attend Visit 8 to begin Course 4. Some patients also received additional courses between Visit 6 and Visit 8 (See Section 9.8.1).

The off-treatment period between Visit 6 (end of Treatment Course 3) and Visit 8 (start of Treatment course 4) may have been longer than 28 days for some patients.

All patients were instructed to administer a bronchodilator before taking their AI. Patients were instructed to refrain from using their bronchodilator for 6 hours before each visit unless used for rescue. *Patients were instructed to administer a short-acting bronchodilator in the clinic approximately 15 minutes before spirometry.* Patients were deemed treatment compliant if they used at least 80% of the vials. Patients were to be withdrawn from the study if they used less than 50% of the assigned treatment vials at the end of a treatment course.

All adverse events (AEs) were assessed by the investigator. Patients were also examined by the investigator or qualified member of the clinical staff.

No inferential analyses were planned; no hypotheses were tested. Stratification by age or disease severity was not undertaken. Summaries of categorical data were presented using counts and percentages. Summaries of continuous data were presented using mean, standard deviation (SD), median, minimum, maximum and numbers of patients and quartiles. Data collected at early termination were included in the analyses and assigned to what would have been the next scheduled visit. Microbiology and disease-related endpoint data were not imputed. Missing severity or relationship of safety data was assumed to be 'severe' and 'probably related'.

For system organ class (SOC) and preferred term and for summary of adverse events by severity, counting was done by patient and event separately. For counts by patient, a patient was only counted once within each SOC and once within each preferred term. The Fisher's exact test was used to compare the twice daily and three times daily groups for overall treatment regimen effect. Microbiology analyses were conducted on the Safety population. Data collected a Visit 1 served as the baseline for microbiology parameters.

Duration adjusted AEs were calculated per patient-month which was defined as a 28 day period. Kaplan-Meier summary statistics were calculated and the Log-Rank test was used to compare treatment regimens. Time to events was calculated in days from Visit 1 to the event.

Up to 400 patients were eligible for enrolment. Roughly two thirds of eligible patients (274) were enrolled and included in the Safety Population: 85 in the AI twice daily (bd) regimen and 189 in the AI three times daily (tds) regimen. Patients from CP-AI-005 continued prior dose regimens, either twice or three times daily. Patients from CP-AI-007 were all dosed three times daily. The numbers completing 9 treatment courses comprised 46/85 (54%) of the twice daily treatment group and 120/189 (63.5%) of the three time daily treatment group. "Personal or administrative" was the most common reason for discontinuing; this included patient withdrawal of consent but other reasons were not clarified. The majority of patients in all groups were white (93.4%); 55% were male. Approximately 80% were at least 18 years of

age. Children aged ≥ 6 to 12 years numbered 8/85 (4.7%) for the twice daily regimen and 14/189 (7.4%) for the three times daily regimen. Baseline characteristics were fairly well balanced between groups.

Efficacy Results

Treatment compliance was reported for 84.7% of the twice daily group and 82.0% of the three times daily treatment group.

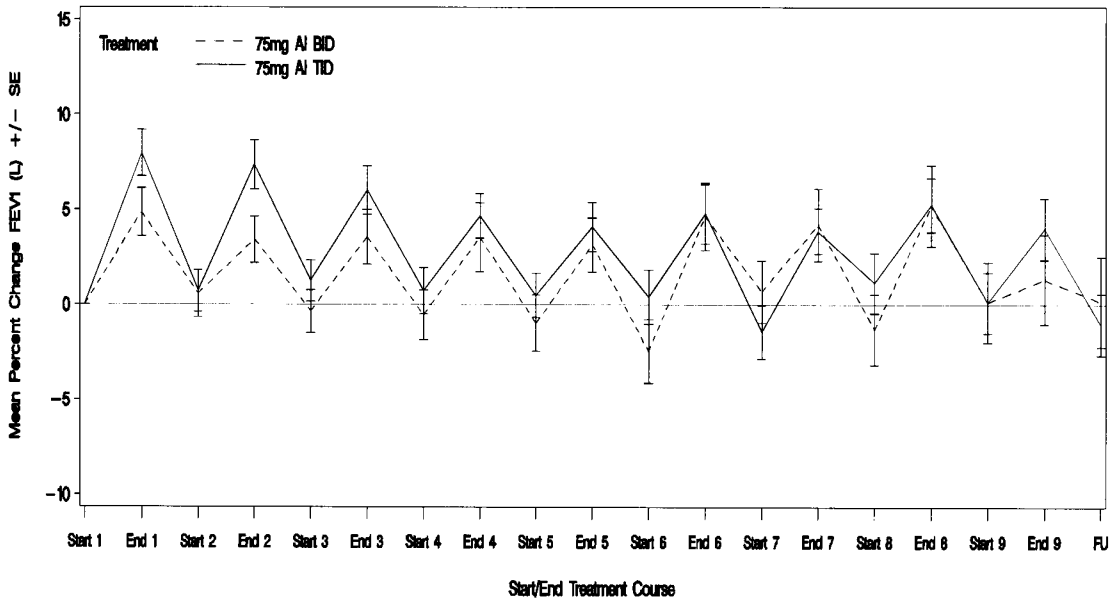
FEV_1

Percent change in FEV_1 is summarised in Table 21.

As shown by the size of the standard deviation in comparison to the means, there must have been a very wide variation in the results. Figure 6 shows the percent changes in FEV_1 from Visit 1 for the twice daily and three times daily groups. Increases in FEV_1 are seen at the end of each treatment course, but note that the standard error is shown in this figure, not the confidence interval which was not reported.

Airway reactivity results were demonstrated by FEV_1 measurements before and 30 minutes following AI administration. It would appear that overall there was a tendency for mean and median FEV_1 to fall slightly after tds administration of AI, even with prior administration of bronchodilator approximately 15 minutes before assessing FEV_1. The sponsor considers that airway reactivity (mean percent change in FEV_1) was similar between groups and did not worsen with repeated course of AI. However, over the course of the study, considerably more than 20% of patients dropped out of the trial.

Figure 6: Percent Change in FEV_1 (L) from Visit 1 for AI bd and AI tds vs. Visit: ITT Population



Source: Table 14.2.1.6, Listing 16.2.7.2, and Figure 14.9.1.5.

Mean values ± SE

Table 21: Percent Change from Visit 1 in FEV_1 (L): ITT Population

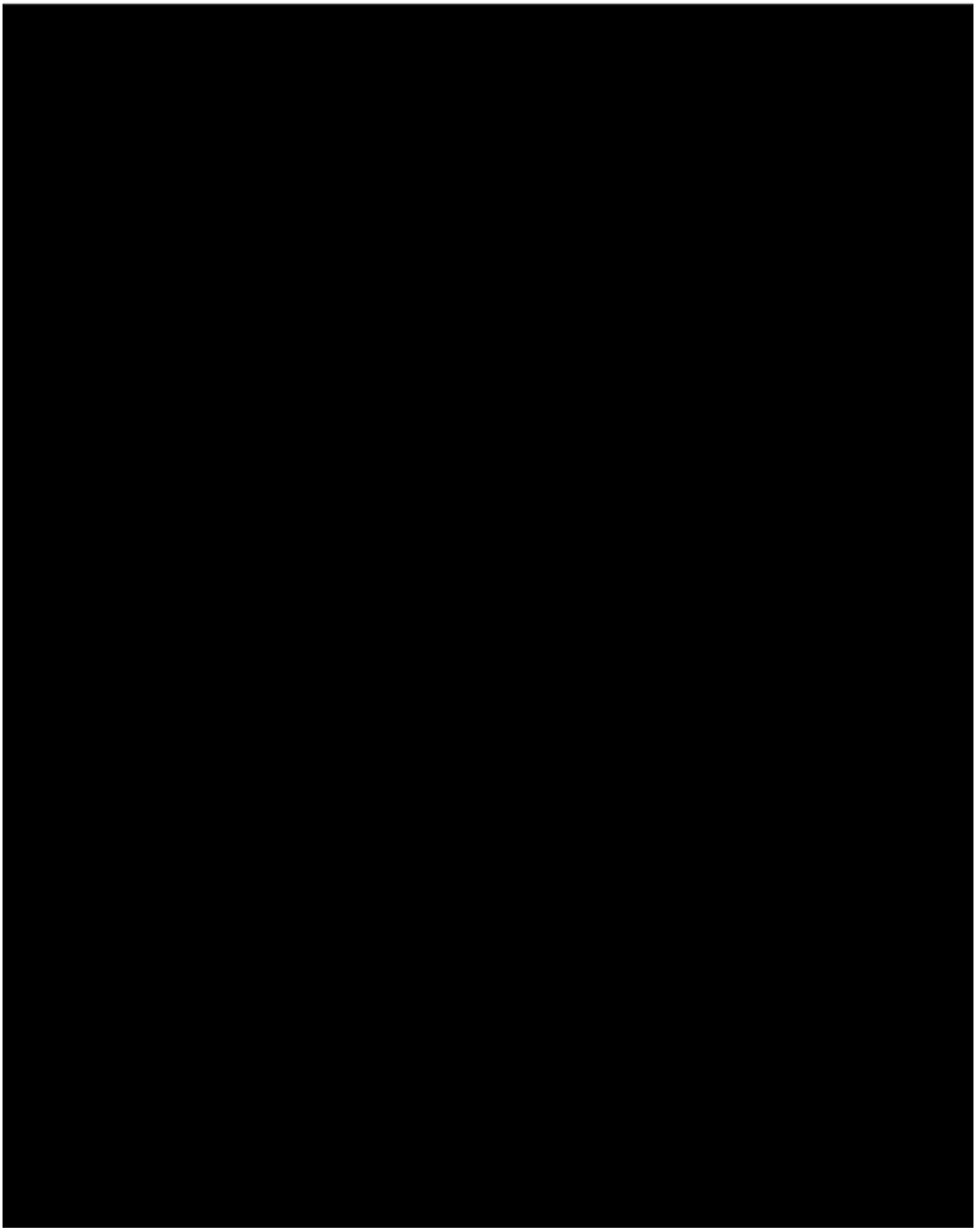


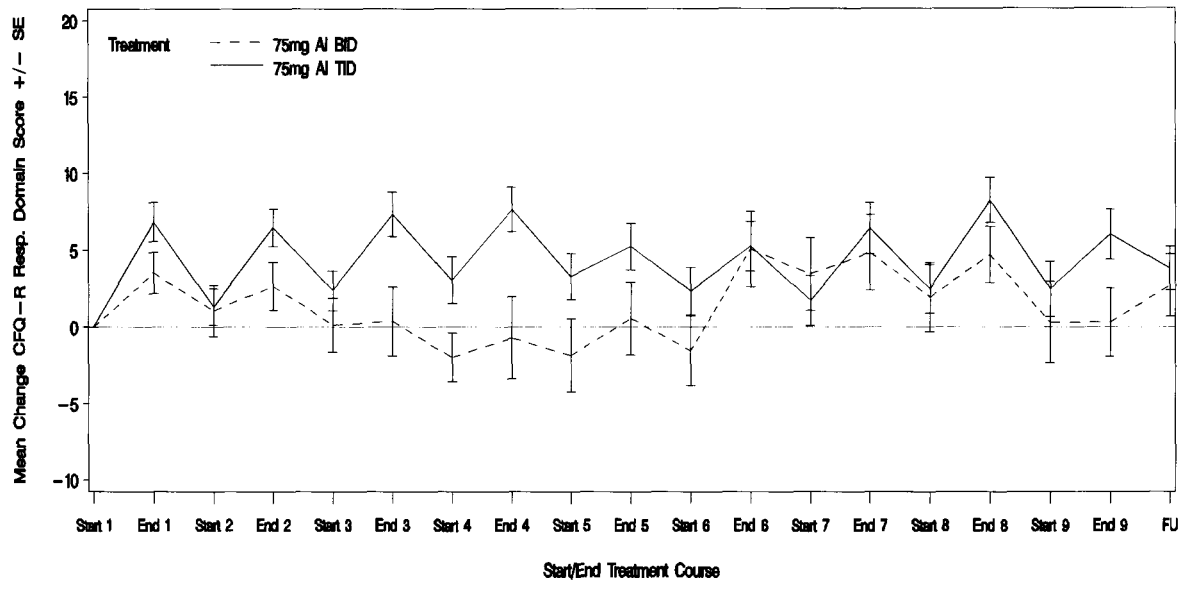
Table 21: Percent Change from Visit 1 in FEV_1 (L): ITT Population (Continued)

[redacted]

CFQ-R

The mean change in the CFQ-R respiratory symptoms domain scores from baseline was greater at the end of each of the nine treatment courses in the tds group than in the bd group (Figure 7). Categorised change from baseline shows the percent recording worsening to be greater at the start of treatment than at the end of treatment, but there was still a sizeable proportion recording a worsening of score.

Figure 7: Absolute Change from Visit 1 in CFQ-R Respiratory Symptoms Domain Score for the bd and tds Groups vs Visit: ITT Population

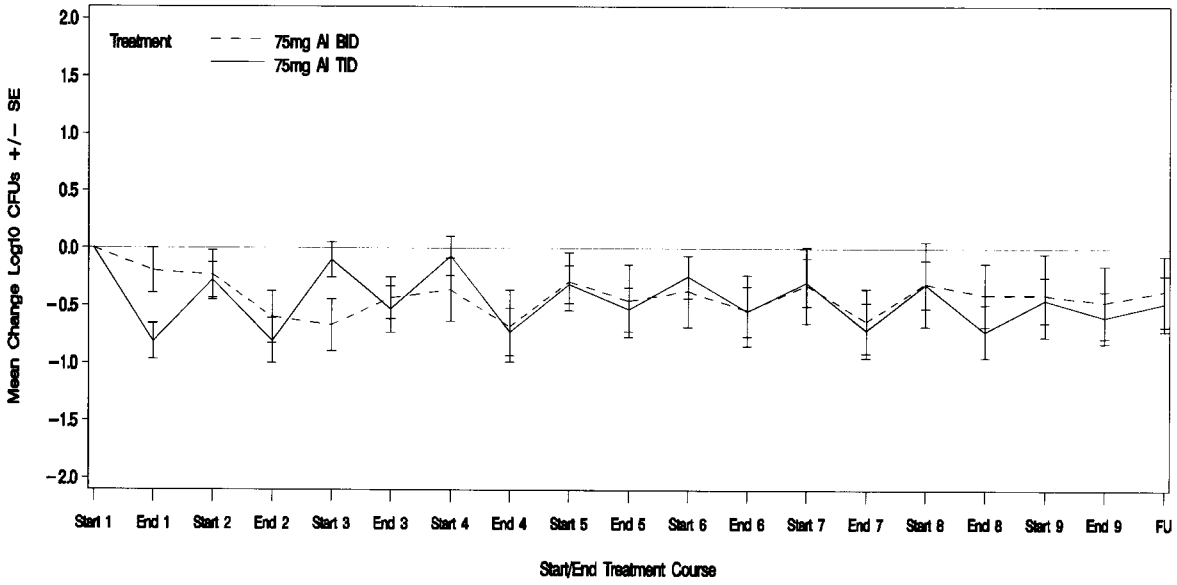


Source: Table 14.2.2.2.3 and Figure 14.9.2.2.
Mean values ± SE

PA Colony Forming Units (CFUs) in Sputum

The changes from baseline in $\log_{10}$ PA CFUs in sputum are shown in Figure 8. Standard deviations are large in comparison to the means and standard error rather than confidence interval is shown in the figure.

Figure 8: Absolute Mean Change from Visit 1 in Log_{10} PA CFUs for AI bd and AI tds vs. Visit: ITT Population



Source: Table 14.2.9.2 and Figure 14.9.3.2.
Mean values ± SE

Hospitalisations

The number of patients hospitalised over time is summarised in Table 22. The number of hospitalisations per patient ranged from 1 to 13. The most common cause of hospitalisation was lower respiratory tract infection. The tds group reported proportionately more hospitalisations than the bd group. A higher SAE rate was noted for the tds group compared to the bd group. A common reason for respiratory hospitalisation was a decrease in FEV_1.

Table 22: Overall summary of Hospitalisation[a]: ITT Population

Hospitalization Endpoint	AZLI Regimen BID (N = 85)	AZLI Regimen TID (N = 189)	Total (N = 274)
% of days hospitalized[b]	2.02	2.83	2.58
Number of Patients Never Hospitalized n (%)	48 (56.5)	90 (47.6)	138 (50.4)
Withdrew Early n (%)	13 (15.3)	24 (12.7)	37 (13.5)
Completed Study n (%)	35 (41.2)	66 (34.9)	101 (36.9)
Number of patients hospitalized at least once, n (%)	37 (43.5)	99 (52.4)	136 (49.6)
Number of Patient Years[c]	95.46	221.02	316.48
Number of Hospitalizations	66	226	292
Hospitalization Rate per Patient Year[d]	0.691	1.023	0.923
Total number of respiratory hospitalizations	62	211	273
Respiratory Hospitalization Rate per Patient Year[e]	0.649	0.955	0.863
Number of hospitalization days[e]			
Mean (SD)	8.29 (27.60)	12.08 (21.32)	10.91 (23.46)
Median	0.00	0.00	0.00
Minimum	0.0	0.0	0.0
Maximum	245.0	132.0	245.0
n	85	189	274

Source: Table 14.2.4.1 and Listing 16.2.9.1.

a Hospitalization included all hospitalizations recorded as a serious adverse event lasting more than one calendar day, or any death (excl. hospitalizations after completion or withdrawal).

b Percent of days hospitalized is calculated as the sum of all hospitalization days divided by the sum of all patient study days.

c Number of patient years is calculated as the sum of all days on study divided by 365.25.

d Hospitalization rate is calculated as the number of hospitalizations divided by the number of patient years.

e Number of hospitalization days for a patient.

Missed School/Work

The mean percentage of days missed was 2.0% for the bd group and 3.19% for the tds group. The percentage of patients who missed school/work was 60.0% for the bd group and 60.3% for the tds group.

Time to Intravenous Antibiotics

The median time to intravenous anti-pseudomonal antibiotics was 276 days for the bd group (95% CI 217, 316) and for the tds group 232 days (179, 288).

Sponsor's Conclusions regarding Efficacy

The sponsor states that there was an apparent dose response with AI for improvement in lung function with greater mean percent increase in FEV_1 (L) over the nine treatment courses in the tds regimen that in the bd regimen. It is also stated that "since the natural history of PA infection is progressive loss of lung function, the maintenance of lung function above baseline over time is remarkable." The CFQ-R Respiratory symptoms domain scores mirrored the FEV_1 changes.

Safety

Extent of exposure is shown in Table 23. Exposure was consistent across multiple courses of treatment.

Table 23: Cumulative Extent of Exposure: Safety Population

Almost 98% of both treatment groups reported at least one adverse event (Table 24). Approximately 35% of the twice daily group and 42% of the three times daily group reported at least one drug-related adverse event. Approximately 8% of patients withdrew as a result of an AE in the twice daily group and 20.1% in the three times daily group. One patient in the twice daily group died; one patient in the three times daily group died after withdrawing from the study. Both deaths were considered unlikely to be due to study therapy: one was due to haemoptysis and the other to end stage renal failure, calciphylaxis and sepsis.

The most common treatment-emergent AEs were cough and productive cough. Other common treatment-emergent AEs included exercise tolerance decreased, respiratory tract congestion, pharyngolaryngeal pain, pyrexia, fatigue and decreased appetite.

Treatment emergent AEs with incidence≥ 10% are summarised in Table 25. Adverse safety findings were confounded by indication and the lack of controls, lack of blinding and lack of stratification, making interpretation difficult. The differences seen in cough, pharyngolaryngeal pain and pyrexia may have been due to common childhood viral illnesses. Four patients experienced pyrexia considered to be drug related.

Table 24: Overall Summary of Treatment-emergent Adverse Events for the Study as a Whole: Safety Population

	AZLI Regimen		
	BID N= 85) N (%)	**TID (N = 189) N (%)**	**Total (N = 274) N (%)**
Patients reporting at least one AE	83 (97.6)	185 (97.9)	268 (97.8)
Patients reporting at least one drug-related AE[b]	30 (35.3)	79 (41.8)	109 (39.8)
Patients reporting at least one SAE	38 (44.7)	99 (52.4)	137 (50.0)
Patients reporting at least one drug-related SAE[b]	2 (2.4)	6 (3.2)	8 (2.9)
Patients reporting at least one severe AE	26 (30.6)	78 (41.3)	104 (38.0)
Patients with study drug withdrawn as a result of an AE	7 (8.2)	38 (20.1)	45 (16.4)
Number of patients who died	1 (1.2)[a]	0	1 (0.4)[a]
Number of AEs	2069	5368	7437
Number of drug-related AE[b]	137	286	423
Numbers of SAEs	152	510	662
Number of severe AEs[c]	79	274	353

a One patient died approximately 1.5 months after completing 8 courses of AZLI. A second patient died approximately 1.5 months after withdrawing from the study. The SAEs reported for both patients were considered unlikely to be related to the study drug by the investigators.
b Drug-related AEs are those events with a causality of possible or probable
c Severe AEs are those judged by the investigator to be severe in intensity

The numbers reporting at least one SAE was 99 (52.4%) in the tds group and 38 (4437%) in the bd group with no apparent relationship to periods on and off treatment. The percentage reporting at least on severe AE was 30.6% in the bd group and 41.3% in the tds group. The most frequent SAEs adjusted for study duration and compared to pooled placebo groups are summarised in Table 26. However, the pooled placebo results were historical and collected over a much shorter study duration and the evaluator considered that inhaled lactose would not necessarily be inert. The incidence of serious AEs is summarised in Table 27.

The percentage of patients who withdrew from the study as a result of an AE was 7.1% for the bd group and 11.1% for the tds group. There were also summaries of airway reactivity. There were 23 patients, 9 in the bd group and 14 in the tds group who had $\geq$ 15% decrease in FEV_1 on at least 1 occasion. Two of these patients withdrew from the study: one patient was withdrawn from study treatment after receiving the first dose of AI, associated with a decrease in FEV_1 of 28% considered due to study drug intolerance. The second patient requested withdrawal on Day 112 for post-dose chest tightness. This patient experienced acute decreases in FEV_1 of 21%, 16% and 19% at Visits 1, 2 and 3.

The investigators claim a greater reduction in WBC and neutrophils over time in the group treated three times daily, however, the evaluator has trouble discerning a marked difference, and considerable spread of data is suggested by the relatively large standard deviations. Overall 28 haematology results were reported as AEs, though none were considered study drug related.

Analysis of serum chemistry results generally revealed no concerning trends, however the overall number with a shift to high ALT was 30/264 (11.4%), to high AST was 22/262 (8.4%) and to high serum glucose 45/264 (17%). Chemistry results for 60 patients (16 bd and 44 tds) were reported as AES, mostly mild to moderate in severity. Twelve serum chemistry AEs reported for 9 patients were considered possibly related to AI.

Table 25: Treatment-emergent Adverse Events with Incidence Rate of 10% or Higher in Either Treatment Regimen for the Study as a Whole: Safety Population

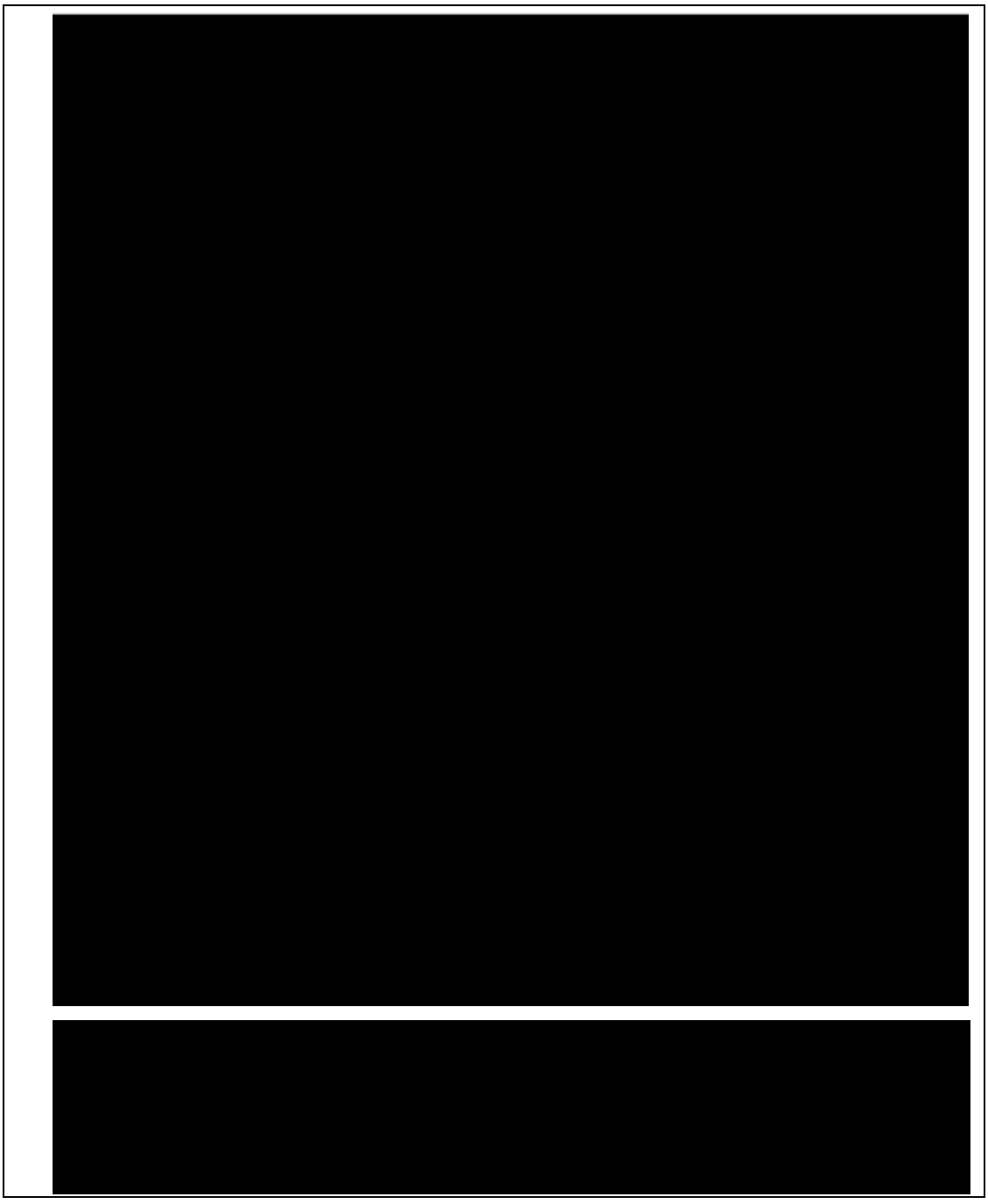
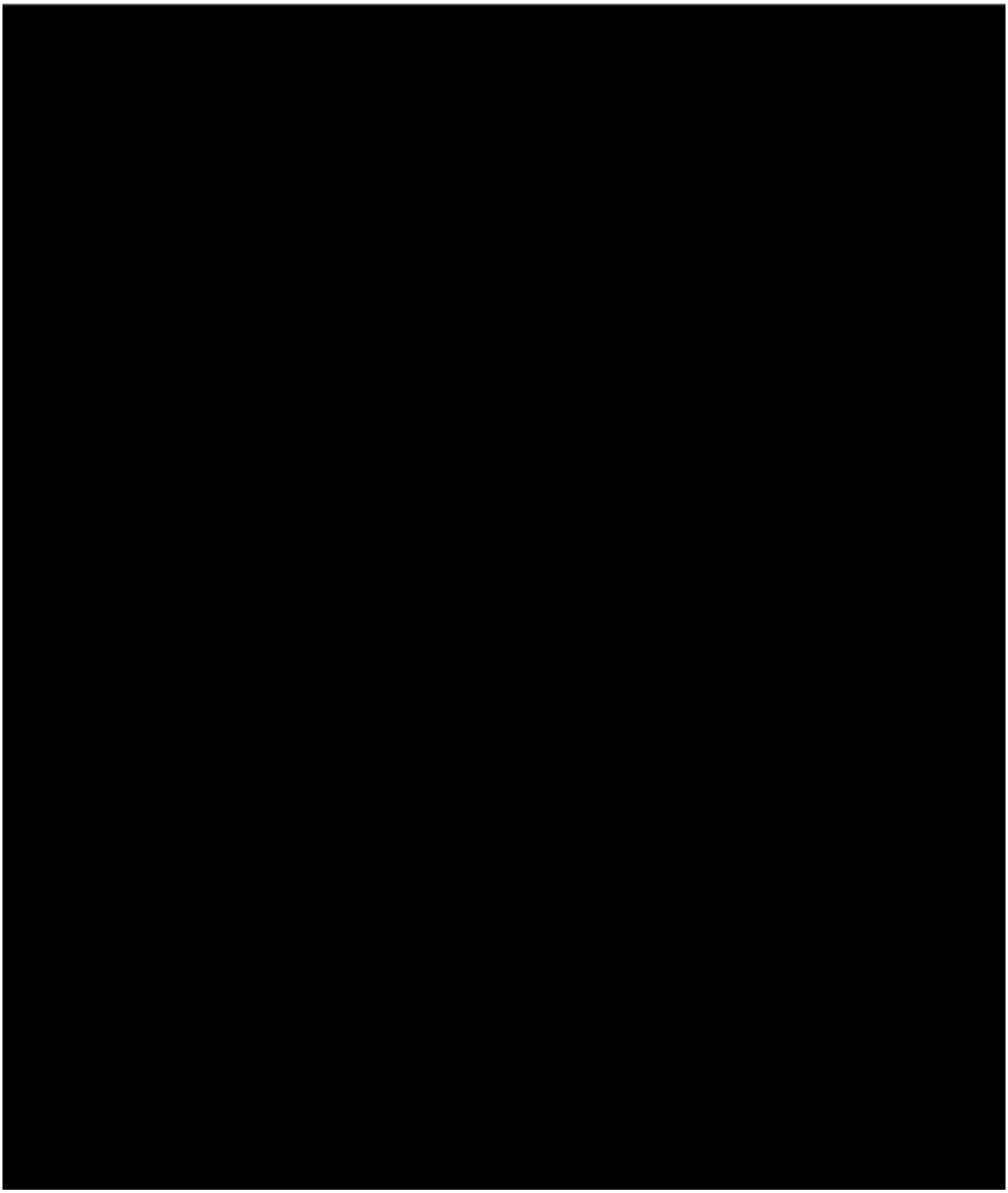


Table 26: Most Frequent SAEs[a] Adjusted for Study Duration

Table 27: Serious Adverse Events with Incidence Rate of 1% or Higher for the Study as a Wholes: Safety Population



Clinical Microbiology

Pseudomonas aeruginosa

At baseline PA was isolated from 94% of patients treated twice daily and 95% of those treated three times daily. Inconsistencies noted regarding the presence or absence of *PA* throughout the study were considered most likely due to variations in sampling technique or the patients' ability to produce sputum.

Changes in MIC of aztreonam for PA isolates were summarised. The MIC_{50} and MIC_{90} reported for all *PA* isolates appeared to increase over the course of the study, returning to baseline at the very last visit. Changes in the MIC_{50} for the tds group were not marked; change in the MIC_{90} did occur with increases $\geq$ 4 fold being reported intermittently. These changes are difficult to interpret in the absence of controls and with the well established difficulty in reporting of susceptibility of different forms of PA and the difficulty of obtaining any specimen, let alone satisfactory specimens as reflected in the variable numbers of specimens included in each visit result.

The change from Visit 1 in the MIC of aztreonam for PA isolate with the highest MIC from each patient was summarised. The percent with increased MIC at the end of treatment appeared to rise over the course of the study from 26.3% to 38% at the end of treatment course 9. Interpretation is difficult, though reason and experience suggests that resistance will develop with time and exposure.

MIC_{50} data remained unchanged for tobramycin. There was a fall in the MIC_{90} observed in the bd group, though not consistently in the tds group. There was no significant increase in the MIC_{50} of the following: amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, meropenem, piperacillin, tobramycin and ticarcillin/clavulanate apart from transient increases noted for ceftazidime, piperacillin and ticarcillin/clavulanate in the bd group and a more persistent increase for meropenem in the bd group for the PA isolates with the highest MICs from each patient.

Staphylococcus aureus

There were slight fluctuations in the percentage of patients testing positive for *S aureus* following repeated dosing up to nine courses of AI in both treatment groups. At visit 1, *S. aureus* was present in 39% of the bd treated patients and at the end of the ninth visit it was detected in 33.3%. For the tds group, S. aureus was present in 35.1% at the first visit and 42% at the ninth visit.

At first visit, 31% of the bd group had MS*SA* detected and 8.3% had MR*SA* while in the tds group 19.7% had MS*SA* at baseline and 15.4% had MR*SA* detected. Following nine courses, the percentage of patients from the bd group with MS*SA* was 22% and MR*SA* was 11.1% compared to the tds group in which 26% had MS*SA* while 16% had MRSA detected. At no time did the percentage of patients with MS*SA* and MR*SA* deviate significantly from baseline.

Burkholderia cepaci complex

B. cepacia was not found in any of the patients in the bd group and did not emerge over the course of the study. Only one in the tds group had *B cepacia* at visit 1; treatment emergent *B cepacia* was isolated intermittently in samples from 3 other patients in this group during the course of the study.

Stenotrophomonas maltophilia

S maltophilia was present at visit 1 in 15.5% of the bd treated patients, with a range of 7.8% to 18.8% testing positive during the nine treatment courses. In the tds group, 7.6% tested positive at visit 1, with a range of 7.6% to 13.8% testing positive during the nine treatment courses

Achromobacter xylosoxidans

There was no notable change in the percentage of patients testing positive for *A. xylosoxidans* following repeated dosing with up to nine courses of AI. *A. xylosoxidans* was present in 9.5% of the bd patients at visit 1 and ranged between 5.7% to 10.9% over the course of the study.

Of the tds group, 7% tested positive at visit 1 with a range of 5% to 11.6% testing positive over the study period.

Candida spp

At baseline, 60.7% of the bd group and 73% of the tds group had *Candida* species isolated. At the end of the 9 course study, the prevalence was 84.4% in the bd group and 83.5% in the tds group.

Aspergillus spp

At baseline 17.9% of the bd group and 22.2% of the tds group tested positive for *Aspergillus* species. At the end of the study, 20% of the bd group and 22.3% of the tds group had positive culture for Aspergillus spp.

Paediatric Results

FEV_1 % Change from Day 1

There was little data pertinent to the paediatric age group. Between the start of treatment Month 6 and the end of treatment Month 7, the number of patients with FEV_1 results reported fell below 80% in the overall group < 18 years and both subgroups≥ 6 to ≤ 12, and > 12 to < 18 years. Up until this time the mean results demonstrated the same swing between increased FEV_1 at the end of treatment and decrease at the beginning of the next course of treatment. The standard deviations were very large in comparison to the mean; mean and median values suggested skewed data; the range of results was very broad.

Age Less than 18 Years

There were a total of 55 patients in this age group, 19 in the pooled bd group and 36 in the pooled tds group. The number of participants with FEV_1 results available for the entire study period was a total of 33 (60%), 10 (53%) in the bd group and 23 (64%) in the tds group. By the end of last month of treatment with participating numbers at or above 80%, (Month 5), the absolute change in FEV_1 from baseline was: mean 0.83, median 2.67, SD 9.5254, Min - 27.76, Max 16.74. The percent change from baseline was: mean 3.05, median 4.94, SD 15.868 Min - 32.24 Max 46.08

Age 6 to 12 Years

There were a total of 18 patients in this age group, 4 in the pooled bd group and 14 in the pooled tds group. The number of participants with FEV_1 results available for the entire study period was a total of 9 (50%), 1 (25%) in the bd group and 8 (44%) of the tds group. By the end of last month of treatment with participating numbers at or above 80%, (Month 5), the absolute change in FEV_1 from baseline was: mean 0.1.08, median 2.38, SD 9.400, Min - 14.73, Max 16.74. The percent change from baseline was: mean 2.29, median 2.88, SD 15.438 Min - 21.65 Max 32.13

Age 13 to 17 Years

There were a total of 37 patients in this age group, 15 in the pooled bd group and 22 in the pooled tds group. The number of participants with results available for the entire study period was 24 (65%); 9 (60%) in the bd group and 15 (68%) in the tds group. By the end of last month of treatment with participating numbers≥ 80%, (Month 5) , the absolute change in FEV_1 from baseline was: mean 0.70, median 2.84, SD 9.323, Min - 27.6, Max 16.57. The percent change from baseline was: mean 3.44, median 6.40, SD 16.307 Min - 32.24 Max 46.08.

Adverse Events

The number of children reporting at least one drug related adverse event was 32% of all patients less than 18 years, 32.4% of those between 6 and 12 years and 22.2% of those over 12 and less than 18 years. Hospitalisations were summarised, but no other data specific to the paediatric patients could be located.

Clinical Summary and Conclusions

Initial Clinical Evaluation

Studies were conducted in patients with stable cystic fibrosis with airways colonization by *Pseudomonas aeruginosa*. Inhaled alternatives currently used in Australia include inhaled tobramycin and inhaled colistin (off label use of intravenous preparation), but alternatives are required because of increasing resistance of gram negative organisms to antibiotics in this patient group. A different formulation of aztreonam is approved for use in Australia for systemic administration, and is generally well tolerated.

Systemic exposure following inhalation of aztreonam lysine was variable, but much lower than exposure following intravenous dosing. There were considerable variations in sputum concentrations of aztreonam lysine following inhaled aztreonam, but the clinical significance of this finding is uncertain.

Phase 2/3 studies were conducted in patients >6 years of age with stable disease. Outcome measures used clinically relevant subjective and objective outcome measures, including symptom scores and FEV_1. Studies demonstrated a small but greater improvement in average symptom scores and FEV_1 in inhaled aztreonam-treated patients compared to those receiving placebo during the treatment course. However, a significant proportion of patients receiving placebo also had improvements in symptom scores. The magnitude of benefit in FEV_1 is similar to that in studies of other inhaled agents, such as inhaled tobramycin. There were no long term positive or negative trends in symptoms scores or FEV_1 evident with repeated 28-day courses of inhaled aztreonam.

There was limited data on other clinically relevant endpoints, such as hospitalization, the need for intravenous antibiotics, superinfection with resistant organisms and longer term outcomes. Further, studies did not compare inhaled aztreonam with other inhaled antibiotics. The difficulties in conducting such studies in a relatively limited population with this orphan disease, often colonized with organisms resistant to multiple antibiotics, is acknowledged. Safety and efficacy have not been demonstrated in patients colonized with B. cepacia, patients following lung transplantation, patients <6 years of age and patients with predicted FEV_1<25% or >75%.

The difficulties in ascribing adverse events to inhaled aztreonam in this patient group are also acknowledged. Local irritation, including cough, nasal congestion and wheezing, were commonly reported but significant allergic phenomena such as rash and bronchospasm appear to be uncommon. Fever was reported in paediatric patients; the cause of this is unclear.

The US Food and Drug Administration have recently declined to approve the sponsor's New Drug Application for inhaled aztreonam. The reasons for this decision are not yet known, but are not believed to be due to concerns regarding safety.

The evaluator's concerns focus on the following areas:

- Preclinical studies in animals suggest transient squamous metaplasia at high doses; this significance of this finding in humans is not clear.
- Inhaled aztreonam was administered using a specific electronic nebulizer: the safety and efficacy of its use by other administration devices has not been established. This is reflected in the proposed product information.
- The duration of exposure and the number of patients participating in studies is relatively low; there is limited power to detect uncommon but severe adverse events, and long term safety and efficacy has not been established, particularly with respect to pulmonary toxicity. Phase 2/3 studies have only determined efficacy and safety in placebo controlled

studies up to 28 days. However, intravenous aztreonam has a long history of use with no significant safety concerns.

- The magnitude of benefit, based on subjective and objective endpoints, appears to be small with a large variation in response between patients. Analyses were not presented on factors that account for this variation. However, the mean change in FEV_1 during the treatment course appears to be similar to that reported for other inhaled antibiotic agents.
- The proportion of patients reporting improvement in symptom scores was greater in the group receiving inhaled aztreonam, but the proportion of patients reporting improvement in objective measures (clinically significant improvement in FEV_1, clinically significant reduction in sputum bacterial concentrations) was not reported.
- Studies were conducted in a very specific patient group; the results may not be generalisable to patients with bronchiectasis not due to cystic fibrosis, and patients colonized with other respiratory pathogens (including B. cepacia).
- Studies were conducted in patients with cystic fibrosis without evidence of acute exacerbations due to infection; there are no data on its use in patients with active infection.
- Fever was reported as an adverse event in a significant proportion of paediatric patients. Although generally assessed as mild and unrelated to the study drug, the cause of fever was not clear.

The clinical evaluator recommended that inhaled aztreonam be approved for use for the following indication:

> *Aztreonam lysine for inhalation is indicated for symptom relief in patients with cystic fibrosis with evidence of airways colonization or infection with Pseudomonas aeruginosa*.

Approval should be conditional on the receipt of analyses demonstrating a higher proportion of patients with improvements in objective outcome measures (clinically significant improvement in FEV_1, clinically significant reduction in sputum bacterial concentrations), as well as post-marketing surveillance for adverse events, results of further clinical trials and analyses presented to the US FDA, and long-term efficacy and safety data.

Supplementary Clinical Evaluation

The submitted study, unblinded, uncontrolled and lacking stratification by age or disease severity, was considered flawed in design. Up to 400 patients from the previously evaluated Studies CP-AI-005 and CP-AI-007 were eligible for enrolment in Study CP-AI-006. Of these, 274 patients were enrolled: 85 in the AI bd regimen and 189 in the AI tds regimen. Approximately 80% of patients were at least 18 years of age. Children aged $\geq$ 6 to 12 years accounted for 4.7% for the twice daily regimen and 7.4% for the three times daily regimen proposed for registration.

Fifty four percent of the twice daily treatment group and 63.5% of the three time daily treatment group completed the 9 treatment courses. “Personal or administrative” was the most common reason for discontinuing; this included patient withdrawal of consent but other reasons included in this category were not clarified.

In support of efficacy, Figure 6 shows a saw tooth pattern of increase in FEV_1 by the end of treatment phase and decrease after the 28 days off treatment, with apparently better results for the tds group. Over the course of the study there appears to be a gradual decline in the FEV_1 results. Standard errors were very large in comparison to the mean reflecting a wide range in

the results; confidence intervals were not reported. The lack of a control group makes all results of this study difficult to interpret. The lack of blinding is also a problem. The rise in the FEV_1 could have been confounded by greater compliance with all modes of treatment when patients were more actively involved in the study process. The loss of between 36.5% to 46% of patients by the end of the study also makes the results difficult to interpret, as patients who might otherwise adversely affect the result may not be included.

In assessing airway reactivity, mean and median FEV_1 results show a small but consistent drop in the tds group 30 minutes after treatment despite the use of a bronchodilator before AI administration and approximately 15 minutes before FEV_1 measurement if the submission is being correctly interpreted. Twenty-five patients recorded a drop of $\geq$ 15% at least once during the course of the study and two patients discontinued because of drops of 21% and 28%. The proposed formulation would appear to have the potential to induce bronchospasm.

Because of the lack of age stratification it is not possible to determine whether the youngest, smallest patients for whom the dose was relatively large, were more or less likely to report a fall in FEV_1 after treatment. It was noted that the dose for the study was chosen because in the Phase II clinical trial AI-003 a trend was noted for the higher dose of 225 mg to be associated with increased respiratory symptoms attributed to treatment.

The mean change in the CFQ-R respiratory symptoms domain scores from baseline showed the same saw toothed pattern reported for FEV_1, again with the tds group appearing to do better than the bd group. The unblinded nature of the study, the lack of controls and the number of patient drop-outs again makes interpretation difficult and the categorical analysis suggests that a significant proportion of patients felt worse after treatment, though it is not possible to say whether the same patients consistently felt worse.

Other results included in the efficacy section, hospitalisation, days off school/work and time to intravenous treatment presented difficulties in interpretation due to the design of the study. It was noted that the mean time to use of intravenous anti-pseudomonal drugs was shorter in the tds group than the bd group, and the upper limit of the 95% CI for the tds group was not much more than the lower limit of the CI for the bd group. This is in keeping with the higher rate of hospitalisation and higher incidence of SAEs reported in the tds group than the bd group. However the sponsor considered that greater increases in FEV_1 in the tds group during the on-treatment periods, with subsequent declines during the off-treatment intervals, most likely explained the difference in rates of hospitalisation (and SAEs) between the two groups.

Eradication of PA was not expected. Inconsistencies were considered most likely due to variations in sampling technique or the patients' ability to product sputum. PA is known to be hard to characterise and various forms within the same patient may have very different sensitivity characteristics; thus interpretation of the results is difficult. It would appear that rapidly accruing resistance was not noted; however experience suggests that resistance will develop with time and continuing exposure.

Results reported for the other organisms; methicillin sensitive and methicillin resistant *S. aureus, B. cepacia, S maltophilia, A xylosoxidans, Candida* species, and *Aspergillus* species did not give rise to concern that overall, organisms not covered by aztreonam would increase in prevalence. However, the population studied was largely adult. Paediatric patients who tend to be colonised with *S. aureus* rather than *PA* may possibly present a different picture. It is not possible to comment on this possibility due to small numbers of children, particularly young children enrolled in the study. Furthermore there was a higher incidence of *B. cepacia* in the tds group. This may have been due to chance. It is notable, however, that a history of

sputum or throat swab culture yielding *B. cepacia* in the previous 2 years was an exclusion criterion.

The most common adverse events were common events associated with the disease. While efficacy in the tds group appeared to be better, drug related adverse events and discontinuations due to adverse events were more common in this group than in the bd group. However, the study was not designed to determine statistically significant differences in safety between groups any more than for differences in efficacy between groups.

The evaluator accepted the position that alternative antibiotics are required for patients who have developed resistance to the currently registered drugs.

It was noted that Cayston has been granted a positive opinion in the European Union for use in adult patients. Details of the scientific discussion was not available to the evaluator, though it was noted that the CHMP took note of "the company's suggestion that the medicine was only intended for use as short term treatment". The CHMP approved indication is as follows:

Cayston is indicated for the suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) age 18 years and older. The primary support for this indication is based on two single 28 day course placebo-controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited (see section 5.1). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Recommendation

Despite the considerable reservations outlined above, the evaluator recommended registration of Cayston for use in both adults and children with documented chronic PA colonisation. The recommendation is contingent on specification in the Indications that the decision is based on limited data, in particular very limited data relevant to use of Cayston in children. Furthermore it was recommended that the first dose be administered in a setting adequately equipped to deal with significant fall in FEV_1 should that occur.

V. Pharmacovigilance Findings

There were no pharmacovigilance data presented with the application.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The drug substance is produced by chemical synthesis. The drug product contains 75 mg aztreonam and 46.7 mg lysine (as buffer), for reconstitution with the supplied diluent (1 mL sterile 0.17% NaCl solution). The osmolality of reconstituted solution is < 550 mOsm/kg which is critical for avoiding bronchospasm when inhaled. Stability data support a shelf life of 24 months at 2-8°C and 28 days below 25°C. Lysine is the only excipient. There is no preservative in the product.

The product was considered at the 123rd meeting of PSC. The issues identified by the Committee have been addressed, including a lower bioburden limit.

There are no outstanding objections to the registration of the product on chemistry and quality control grounds, except for five impurities which have not been adequate qualified at the limits proposed.

Nonclinical

Local toxicological effects were seen in lungs, nasal cavity, and larynx. Systemic toxicity was observed in kidney, liver and endocrine system, consistent with the previously registered intravenous formulation. Histopathological effects were seen adrenal, thyroid and pituitary glands in carcinogenicity studies.

Increased incidence of thyroid adenomas, laryngeal squamous metaplasia and atrophic effect in nasal cavity effects noted in the animal studies were not thought to be relevant to the proposed human use.

Overall, the range of toxicological data available was considered adequate and there were no objections to registration on toxicological grounds.

Clinical

Initial Clinical Evaluation Report (CER)

Pharmacodynamics

Aztreonam is a monobactam antibiotic with activity against aerobic gram-negative bacteria including *Pseudomonas aeruginosa* (PA). Aztreonam is not effective against gram-positive organisms. The proportion of PA strains susceptible to aztreonam varies with population.

The mechanism of action is binding to Penicillin Binding Proteins, leading to disruption of bacterial cell wall synthesis.

In vitro studies report MIC_{50} of ≤ 2 µg/mL for gram-negative bacilli in general, and MIC_{50} of $\leq$ 4-8 µg/mL for PA specifically has been estimated. The NCCLS 2004 guidelines define isolates with a MIC ≤ 8 µg/mL as susceptible and MIC ≥ 32 µg/mL as resistant for gram-negative bacilli.

Development of aztreonam resistance in PA has been reported. Expression of the B-lactamase, *AmpC*, which can be either chromosomal or plasmid-encoded, a decrease in porin synthesis and increased efflux activity are common methods of resistance. Increase in resistance to aztreonam by any of these mechanisms will correlate with increased resistance to other B-lactams. Cross-resistance to other classes of antibiotics has not been reported.

Pharmacokinetics

Aztreonam is administered by inhalation. There was a wide variability in systemic exposure following inhalation. In CF patients, the mean plasma AUC after single 75 mg inhalation was 1629 ± 522 ng.hr/mL. The Cmax was 419 ± 155 ng/mL at 1 hour.

There was no evidence of accumulation following dosing for up to 28 days in Phase 3 studies. The reported serum concentration of aztreonam after 500 mg injection is about 54 µg/mL indicating low systemic exposures with inhalational use.

The estimated elimination half-life was 2.1-2.85 hours, similar to that with intravenous use. The route of elimination is through kidneys, consisting of both filtration and secretion. Aztreonam does not undergo hepatic metabolism.

Sputum concentrations 10 minutes after inhalation of 75 mg dose were also highly variable, ranging from 0 to 6010 µg/mL. The correlation with plasma levels was poor.

No specific drug-drug interaction studies were carried out.

Pharmacokinetics were not examined in renal or hepatic impaired patients but this is accepted with the expected low systemic exposure.

Efficacy

Three completed clinical studies were provided in support of efficacy and safety. The study AI-007 is pivotal. All studies were carried out in patients 6 years old and above and in stable CF disease at the time of treatment; that is, not during exacerbation.

Study AI-007

This was a randomised, double blind, placebo-controlled (n = 84) trial to assess efficacy of 75 mg aztreonam (n = 80) three times daily by inhalation for 28 days. The overall mean age was 29.6 ± 14 years and 22.6% patients were < 18 years age. The lowest age category of 6-12 years comprised about 9% of the total cohort.

Disease severity with respect to pulmonary function (FEV_1) was similar in both groups at baseline. The proportion of homozygous patients in aztreonam arm was 54% compared with 43% in placebo. Overall, 19.3% patients had unidentified genotype. There was some imbalance of *P aeruginosa* susceptibility to aztreonam at baseline. Baseline oxygen saturation was similar in both groups.

A total of 57/84 (68%) placebo and 67/80 (84%) aztreonam patients completed the study. Among the premature discontinuations, the majority were due to adverse events or intolerance in both groups.

Other notable features for this trial include 7-14 days run-in period without anti-pseudomonal treatment and routine use of bronchodilators prior to administration of study drugs.

The primary outcome was change in respiratory symptoms at 28 days measured by CFQ-R (respiratory domain), which is a validated questionnaire for assessment of quality of life in CF. The 4 point scale was normalised on a scale of 0 to 100. A change of 5 points was considered clinically important in consultation with the FDA.

The change in CFQ-R score, after 28 days treatment, was -2.63 vs. 7.08 in placebo and aztreonam arms respectively representing a treatment difference of 9.71 (95% CI: 4.31, 15.11) in favour of aztreonam. By Day 42 (14 days post-treatment) the treatment difference had declined to 6.33 (95% CI 1.22 to 11.43). At 28 days, 56% patients in aztreonam group were categorised as improved compared to 37% in the placebo group.

At 28 days, the change in FEV_1 was -0.038 L vs. 0.151 L in placebo and aztreonam arms respectively representing a treatment difference of 0.188 L (95% CI 0.115 to 0.262 L) in favour of aztreonam. In terms of percentage change in FEV_1, the treatment difference was 10% (95% CI 6 to 14%). As with CFQ-R score, the treatment difference declined nearly by half (6%) 14 days after completion of treatment.

The sputum concentration of PA decreased by 1.45 log units at Day 28 in aztreonam group compared to placebo but returned to baseline level at 14 days post-treatment. This analysis was based on evaluable patients only (61 & 53 patients in placebo and aztreonam arms respectively).

35.7% placebo patients used anti-pseudomonal antibiotics other than aztreonam compared with 17.5% aztreonam patients. The percentage of patients needing hospitalisation was 14.3% and 5.0% in placebo and aztreonam groups respectively.

Study AI-005

In this dose selection study, 75 mg twice daily aztreonam was compared with 75 mg three times daily against placebo for 28 days of treatment in a randomised double-blind fashion. All patients received 28 days of inhaled tobramycin in the run-in period and were allocated to aztreonam 75 mg bd (n = 69), aztreonam tds (n = 66), placebo bd (n = 38) and placebo tds (n = 38). Patients were comparable at the start but less than 50% completed the trial.

The change in CFQ-R at 28 days was 5.10 (95% CI 0.81 to 9.21) in aztreonam compared to placebo (pooled data). The treatment effect for FEV_1 was a median of 2.53 L (95% CI 0.72 to 4.4 L) equivalent to 6.3% (95% CI 2.5 to 10%) in favour of aztreonam.

The median time to requiring an inhaled or intravenous antibiotic was 92 days vs. 71 days in aztreonam and placebo pooled groups respectively.

The PA sputum concentration at 28 days was 0.66 log units lower in aztreonam group compared to placebo but returned to baseline level 14 days post-treatment.

The differences between the 2 aztreonam doses were not reported.

Study AI-003

This supporting study compared aztreonam 75 mg twice daily (n= 38) and aztreonam 225 mg twice daily (n = 33) with placebo (n = 32) for a treatment period of 14 days. There was some imbalance in groups with respect to $FEV_1 < 60\%$ and colonisation with non-susceptible PA at baseline.

No treatment difference in FEV_1 was observed after 14 day for aztreonam 75 mg bd compared to placebo. Aztreonam 225 mg was associated with bronchospasm.

Rollover study AI-006 (interim reports)

This was interim report (n = 207) of repeated courses of inhaled aztreonam (bd or tds) in rollover patients (n = 274). Repeat courses were associated with improvement in outcomes during treatment but were not sustained in off-treatment intervals.

As of cut-off date of 31 August 2007, a total of 3001 patient-months of study exposure have been achieved.

PA was isolated from 93% patients at baseline. The majority of patients experienced no change through first 6 courses of treatment. An increased prevalence of *S aureus* during the first 3 courses was seen but was not sustained in the subsequent courses. An increased prevalence of *Candida spp* was observed.

No change in susceptibility of PA to aztreonam was reported with tds dosing, but there was decreased susceptibility with bid dosing. The proportion of patients with highest aztreonam MIC for PA increased during the first 6 treatment courses, particularly with bid dosing. Concomitant use of beta-lactam antibiotics was allowed during exacerbations.

Improvements in disease-related outcomes (pulmonary function, respiratory symptoms) showed greater response with the tds regimen during treatment periods.

Bacterial Resistance

In controlled clinical studies, the mean change in sputum *Pseudomonas* concentration at Day 28 was higher where baseline MIC was$\leq$ 8 µg/mL although this was not statistically significant. There were no significant differences in the proportion of patients that acquired *S aureus* (9% vs. 8%), *Stenotrophomonas maltophila* (3.7% vs. 1.5%) or *Alcaligenes xylosoxidans* (1.1% vs. 3.6%) at Day 28 compared to placebo. *B cepacia* was isolated from one patient at baseline, was not isolated post-treatment in the 3 efficacy studies and was isolated in one patient in the rollover study.

Safety

The dataset consists of 41 subjects in Phase 1 studies, 289 patients in Phase 2/3 studies and 207 patients in the rollover study.

Most adverse effects reported in the clinical trials were attributable to (or difficult to differentiate from) the underlying disease. The commonly reported adverse effects with aztreonam included cough, nasal congestion and wheezing.

Significant but uncommon effects included rash, allergic phenomena and bronchospasm. Significantly higher occurrence of fever was noted compared to placebo (12% vs. 6%), more so in children compared to adults (13% vs. 8%). The cause of fever in the paediatric population was not clear but did not appear to be related to allergic manifestations.

The second interim report (n = 274) of the rollover study provides comparative estimated rates of common AEs expected with the use of aztreonam as follows:

	Number of Events per Patient-month[b]					
	Integrated Phase 3 Placebo-controlled Studies			Study CP-AI-006		
	Placebo[c] (N = 160) (275 Pt-months)	AI TID[c] (N = 146) (265 Pt-months)	Pooled AI[c] (N = 215) (442 Pt-months)	AI BID[d] (N = 85) (1122 Pt-months)	AI TID[d] (N = 189) (1879 Pt-months)	Total (N = 274) (3001 Pt-months)
Chest discomfort	0.040	0.064	0.059	0.043	0.035	0.038
Cough	0.356	0.412	0.387	0.241	0.295	0.275
Nasal congestion	0.073	0.102	0.097	0.050	0.044	0.046
Pharyngolaryngeal pain	0.062	0.072	0.068	0.049	0.062	0.057
Pyrexia	0.036	0.121	0.088	0.065	0.046	0.053
Rash	0.011	0.011	0.009	0.007	0.006	0.007
Rhinorrhea	0.040	0.042	0.041	0.029	0.043	0.038
Wheezing	0.065	0.087	0.072	0.030	0.029	0.030

Based on this information, there does not appear to be an increased incidence for these effects among the groups, including the comparison of interest between placebo and the three time daily dosing with aztreonam.

Conclusion

The clinical evaluator noted a number of concerns. These were that efficacy and safety were established in placebo controlled studies only up to 28 days of treatment, the magnitude of benefit based on subjective and objective endpoints appeared small, studies were conducted in a very specific group and may not be generalisable to wider patients groups, there are no data on acute exacerbations due to infection and fever was reported in a significant proportion of paediatric patients.

The clinical evaluator recommended that aztreonam lysine for inhalation could be approved for symptom relief in patients with cystic fibrosis with evidence of airways colonization or infection with PA. This recommendation was conditional upon receipt of analyses demonstrating clinically significant improvement in objective outcome measures.

Supplementary Clinical Evaluation Report (SCER)

The sponsor submitted supplementary clinical data consisting of longer–term safety and efficacy data from Study AI-006 study completion in Jan 2009.

Study AI-006 is a Phase 3 open label, follow on study of multiple courses of aztreonam lysine in male and female cystic fibrosis patients who had complied with Studies AI-005 and

AI-007. Subjects received up to nine courses of treatment (28 days courses of Cayston 75 mg administered either bd or tds as a continuation of the regimen in previous studies, followed by a 28 days off-treatment interval).

A total of 274 patients were enrolled, 85 in the bd group and 189 in the tds group. Nine treatment courses were completed by 54% of the bd group and 63.5 % in the tds group. The median days on aztreonam (250) and median days on study (507) were similar in bd and tds groups. Approximately 80% of subjects were 18 years of age or older and 93% were white, non-Hispanic. Mean baseline FEV_1 was around 56% of predicted FEV_1.

Percentage changes in FEV_1 from treatment course 1 at the end of each treatment course were shown in Figure 6 and Tables 20 and 21. Increases in mean FEV_1s were seen at the end of each treatment course. The sponsor reports greater increase in the tds compared to bd groups. There appeared to be trends to a lesser extent of increase in later treatment courses. CFQ-R respiratory symptoms domain scores from baselines are shown in Figure 7 with increases in scores at the end of each treatment course. The increase in scores was higher in the tds compared to bd group. PA CFUs in sputum results are shown in Figure 8. PA CFU mean changes were shown consistently in the tds group with each course of aztreonam.

The tds group had a higher reported rate of hospitalisation compared to the bd group (SCER p9). Median time to IV anti-pseudomonal antibiotics was 276 days (95% CI: 217, 316) for the bd group and 232 days (95% CI: 179,288) for the tds group.

At baseline PA was isolated from 94-95% of subjects. Changes in MIC are presented in Tables 41-49 of SCER. The MIC_{50} and MIC_{90} reported for all isolates appeared to increase over the course of the study. The highest MIC from each patient with PA isolated appeared to rise over the course of the study. There is difficulty in interpretation with a lack of control group, differences in susceptibility for different forms of PA and difficulty in obtaining specimens. Microbiological results for other organisms did not show evidence of increase in prevalence of other species.

Safety

Extent of exposure is shown in Table 23. Almost 98% of both treatment groups reported at least 1 adverse event. Approximately 35% of the bd and 42% of the tds group experienced at least one drug related AE. Study drug withdrawal because of AEs was reported in approximately 8% in the bd group and 20% in the tds group. The percentage who withdrew from the study because of an AE was 7.1% for the bd group and 11.1% for the tds group. Airways reactivity post-dosing was a reason for withdrawal in two patients, including one patient with 28% decrease in FEV_1 after the first dose. One patient died in the bd group. .

Table 24 shows treatment emergent adverse events with cough the most frequent. Table 26 shows SAEs reported at incidence >1%. Analysis of the limited data in the paediatric age group was also presented.

Risk-Benefit Analysis

The initial clinical evaluator recommended approval while expressing concern about long-term safety and efficacy, the small magnitude of the reported benefit, a lack of categorical data for outcomes like FEV_1 & sputum PA and the conduct of trial in stable disease.

The pivotal evidence of efficacy was based on study AI-007. The small size of the study in the context of a rare disease is understandable but the problem was highlighted due to large number of premature withdrawals which were also a feature in other studies.

The primary outcome was patient-reported assessment of quality. However, outcomes more relevant to antibiotic use were also assessed (sputum PA concentration and pulmonary function by FEV_1). The Delegate considered these results acceptable, as similar magnitudes of effect were obtained in the supporting study AI-005.

With respect to the investigation of use in stable disease, it would also have been appropriate to assess use of inhalational aztreonam during acute exacerbations to determine both clinical and microbiological outcomes. This may have provided a trigger for a decision on initiation or further courses of treatment.

The rollover study AI-006 shows a saw tooth pattern of increase in FEV_1 and mean change in CFQ-R scores over cycles of therapy with decrease after 28 days off-treatment. Rapid development of PA resistance to aztreonam was not observed but there was evidence of increase in resistance with time and repeated exposures over the course of the study. The most common adverse events in AI-006 were events associated with the disease. There were more drug related events and withdrawals in the tds group.

The Delegate recognised that for CF, which is a rare and serious disorder, there is a need for more treatment options and the clinical developmental program will have limitations. The Delegate supported registration along the lines recommended in the supplementary clinical evaluation report.

The Delegate supported the proposal for amendment of the product information made in both evaluation reports. In particular, he supported inclusion of a sentence “The first dose of Cayston should be administered in a setting adequately equipped to deal with a significant fall in FEV_1” under ‘Precaution, Bronchospasm’. The Delegate also recommended a number of other Precautions which should be included in the Product Information.

The Delegate also noted that tobramycin for inhalation (TOBI) is registered for use in cystic fibrosis but is not currently marketed in Australia. A comparative clinical study of Cayston versus tobramycin for inhalation is currently being conducted. Submission of the results of ongoing clinical studies should be a condition of registration.

The Delegate proposed to register the product for:

> the management of cystic fibrosis (CF) patients with chronic pulmonary *Pseudomonas aeruginosa* infections.

The primary support for this indication is based on two single 28 day course placebo controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited.

The recommended dose for both adults and paediatric patients 6 years and older is one single use vial (75 mg) administered 3 times a day for a 28 day course (followed by 28 days off Cayston therapy). Each dose should be taken at least 4 hours apart. Cayston is administered by inhalation over a 2 to 3 minute period, using the Altera Nebulizer System.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the following indication:

> *Control of gram-negative bacteria, particularly P. aeruginosa, in the respiratory tract of patients with cystic fibrosis.*
>
> *The primary support for this indication is based on two single 28 days course placebo controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited (see Clinical Trials)*

In making this resolution, the ADEC noted that although there were limitations of Study AI-006 as well as the low numbers of children (and none <6 years of age) enrolled and limited duration of 9 cycles, the Committee recognised that there is a need for more treatment options for control of PA in patients with cystic fibrosis with selection of multidrug resistant organisms in this chronic progressive disease. The clinical developmental program will have limitations because of the orphan nature of the condition. Inhaled Cayston appears to be well tolerated from the safety data available from the studies, with most adverse events attributable to the underlying pulmonary disease. The Committee considered, with regard to the dosing regimen, that there was no significant difference between the bd dosing and tds dosing in study AI-005. In the final analysis of Study AI 006, the mean change in the CFQ respiratory domain score from baseline was greater at the end of many but not all of the nine treatment courses in the tds group compared to the bd group, but there were no other significant difference in efficacy endpoints (change in FEV_1, *Pseudomonas* in sputum, hospitalisation) between tds and bd groups. The Committee considered bd dosing should be further considered for the product as this offer advantages for patient compliance. The ADEC discussed the potential for development of antimicrobial resistance associated with aztreonam for inhalation, which selects chromosomal and plasmid encoded resistance as well as changes in the efflux pump in PA. This would be associated with cross resistance to this antibiotic of other organisms of high importance and to beta lactams and potential selection of important resistant organisms both in individuals treated and those in their environment. The Committee considered there should be limited use of Cayston in the hospital environment because of potential for promotion and spread of antimicrobial resistance.

The specific conditions of registration should include submission of the results of ongoing clinical studies, which include a comparative clinical study of Cayston versus tobramycin for inhalation.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cayston inhalation vial with diluent ampoule containing aztreonam 75 mg indicated for

control of gram-negative bacteria, particularly Pseudomonas aeruginosa, in the respiratory tract of patients with cystic fibrosis.

The primary support for this indication is based on two single 28 day course placebo controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited (see Clinical Trials).

Attachment 1. Product Information

Product Information

CAYSTON® (aztreonam for inhalation)

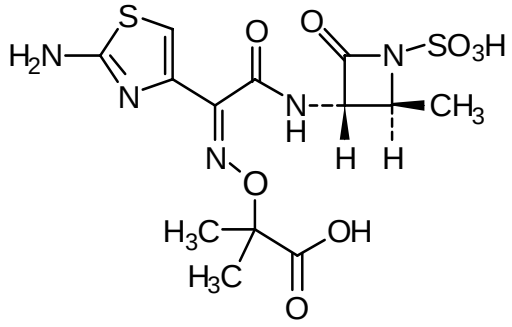
NAME OF THE MEDICINE

CAYSTON

The active substance in CAYSTON is aztreonam.

Aztreonam is a monobactam antibiotic. The monobactams are structurally different from beta-lactam antibiotics (e.g., penicillins, cephalosporins, carbapenems) due to a unique monocyclic nucleus. This nucleus contains several side chains; sulfonic acid in the 1-position activates the nucleus, an aminothiazolyl oxime side chain in the 3-position confers specificity for aerobic gram-negative bacteria including *Pseudomonas spp*., and a methyl group in the 4-position enhances beta-lactamase stability.

Aztreonam is designated chemically as (Z)-2-[[[(2-amino-4-thiazolyl)[[(2S,-3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]caramoyl]methylene]amino]oxy]-2-methylpropionic acid. The structural formula is presented below:



Molecular formula: $C_{13}H_{17}N_5O_8S_2$.

Molecular weight: 435.435

CAS number: 78110-38-0

DESCRIPTION

CAYSTON is a white to off-white powder. It is soluble in water and aqueous solutions. CAYSTON is sterile, hygroscopic, and light sensitive. Once reconstituted with the supplied diluent, the pH range is 4.5 to 6.0.

A dose of CAYSTON consists of one vial containing lyophilized aztreonam (75 mg) and lysine (46.7 mg) and one ampoule containing diluent (1 mL sterile saline [0.17% w/v sodium chloride]). The formulations contain no preservatives.

PHARMACOLOGY

Pharmacokinetics

Sputum Concentrations
Aztreonam concentration in individual patients' sputum exhibited considerable variability. Ten minutes following a single dose of 75 mg CAYSTON, the mean sputum level in 195 patients with cystic fibrosis (CF) was 726 µg/g, which is approximately 10 times that of the aztreonam MIC_{90} for all isolates of *P. aeruginosa* observed at baseline for patients treated with CAYSTON in the Phase 3 placebo-controlled studies (64 µg/ml). Mean sputum levels of aztreonam at Days 0, 14, and 28 of 75 mg three times a day CAYSTON dosing were 984 µg/g, 793 µg/g, and 715 µg/g, respectively, indicating no local accumulation of aztreonam following 3 times a day dosing.

Plasma Concentrations
Aztreonam concentration in individual patients' plasma exhibited considerable variability. One hour following a single dose of 75 mg CAYSTON (at approximately peak plasma concentration), the mean plasma level in patients with CF was 0.59 µg/mL. Mean peak plasma levels at Days 0, 14, and 28 of 75 mg 3 times a day CAYSTON dosing were 0.55 µg/mL, 0.67 µg/mL, and 0.65 µg/mL, respectively, indicating no systemic accumulation of aztreonam following 3 times a day dosing. In contrast, the serum concentration of aztreonam following administration of aztreonam *for injection* (500 mg) is approximately 54 µg/mL.

Elimination
The elimination half-life of aztreonam from serum is approximately 2.1 hours for inhalation administration, similar to what has been reported for aztreonam for injection. Systemically absorbed aztreonam is eliminated about equally by active tubular secretion and glomerular filtration.

Mechanism of Action

Aztreonam exhibits activity *in vitro* against a broad spectrum of gram-negative aerobic pathogens including *P. aeruginosa*. Aztreonam binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis, followed by filamentation and cell lysis.

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.

Microbiology

Susceptibility Testing
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.

Treatment with up to nine 28-day courses (with 28 days between courses) of 75 mg CAYSTON therapy, administered 3 times a day, has not been shown to affect the overall susceptibility of *P. aeruginosa* to aztreonam (Table 1).

Table 1. MIC_{50} and MIC_{90} of Aztreonam for the *P.aeruginosa* Isolate with the Highest MIC from Each Patient (µg/mL)

	n	MIC_{50}[a]	MIC_{90}[a]
Baseline	171	8	256
CAYSTON Course 1	171	8	256
Off Treatment	163	8	256
CAYSTON Course 2	157	8	512
Off Treatment	161	8	256
CAYSTON Course 3	144	16	512
Off Treatment	147	8	256
CAYSTON Course 4	128	8	512
Off Treatment	133	8	512
CAYSTON Course 5	127	8	512
Off Treatment	121	8	256
CAYSTON Course 6	119	16	1024
Off Treatment	118	8	512
CAYSTON Course 7	115	8	512
Off Treatment	117	8	256
CAYSTON Course 8	110	8	512
Off Treatment	111	16	512
CAYSTON Course 9	110	8	1024
Off Treatment	107	8	512

Data for 75 mg CAYSTON administered 3 times a day from the open-label follow-on study, each course 28 days long.
n = number of patients with available data.
[a] Values at end of treatment course; ± 2-fold change in MIC is considered *unchanged.*

Administration of CAYSTON (75 mg) 3 times a day over repeated cycles appears to offer a microbiological advantage over 2 times a day dosing. The susceptibility of *P. aeruginosa* to aztreonam appears to decrease more readily over time with 2 times a day dosing than 3 times a day dosing.

No concerning trends in the treatment-emergent isolation of other bacterial respiratory pathogens (*B. cepacia*, *S. maltophilia*, *A. xylosoxidans*, and *S. aureus*) have been observed following up to nine 28-day courses of 75 mg CAYSTON therapy. Further, no cross-resistance to other antibiotics, including aminoglycosides, quinolones, and beta-lactams, has been observed following up to nine 28-day courses of 75 mg CAYSTON therapy. An increased prevalence of *Candida* species was observed over time in patients treated with several courses of CAYSTON therapy.

In an effort to determine a therapeutic breakpoint specific to CAYSTON, treatment response (measured by improvement in either the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptoms score, Forced Expiratory Volume in one second (FEV_1(L)), or $\log_{10}$ *P. aeruginosa* CFUs in sputum following a 75 mg 3 times a day, 28-day course of CAYSTON) was evaluated in terms of baseline *P. aeruginosa* susceptibility to aztreonam for study AIR-CF1. Among patients with highest baseline aztreonam MIC above the parenteral breakpoint (> 8 μg/mL), 29/31 (93.5%) patients responded to CAYSTON treatment in comparison with 33/38 (86.8%) patients with highest baseline aztreonam MIC below the parenteral breakpoint (≤ 8 μg/mL). Among patients with highest baseline aztreonam MIC ≥ 256 μg/mL (n = 7), all patients responded to CAYSTON treatment in comparison with 55/62 (88.7%) patients with MIC < 256 μg/mL.

Categorical analyses for the relationship between MIC and treatment response provided insufficient evidence to establish a susceptibility breakpoint for CAYSTON. The highest baseline aztreonam MIC may shorten the duration of lung function improvements after completion of CAYSTON treatment. In the Phase 3 placebo-controlled studies, patients with highest baseline aztreonam MIC above or below the parenteral breakpoint demonstrated similar improvements in FEV_1 (L) following a 28-day course of CAYSTON therapy. Two weeks following cessation of CAYSTON therapy, patients with MIC ≤ 8 μg/mL retained substantial improvement in FEV_1; however, FEV_1 dropped to below baseline levels for patients with MIC > 8 μg/mL.

CLINICAL TRIALS

Pseudomonas aeruginosa in Cystic Fibrosis (CF)

CAYSTON was evaluated over a period of 28 days of treatment (one course) in two randomized, double-blind, placebo-controlled, multicenter trials (AIR-CF1 and AIR-CF2) which enrolled patients with cystic fibrosis (CF) who had *Pseudomonas aeruginosa*. To evaluate longer term safety and effects on disease related endpoints, an open-label follow-on study (AIR-CF3) was conducted.

AIR-CF1 was designed to evaluate improvement in respiratory symptoms as measured by the CFQ-R and AIR-CF2 was designed to evaluate the time to need for IV or inhaled antipseudomonal antibiotic therapy. Patients ≥6 years of age and with FEV_1 ≥ 25% and ≤75% predicted were enrolled in both studies. Patients participating in these trials could subsequently receive multiple courses of CAYSTON in an open-label follow-on trial (AIR-CF3). All patients received CAYSTON on an outpatient basis administered with the Altera™ Nebulizer System (for clinical trial use labelled as PARI eFlow® Electronic Nebulizer).

All patients were required to take a dose of an inhaled bronchodilator (beta-agonist) prior to taking each dose of CAYSTON. The trial population was receiving standard care for

CF. Nearly all patients were taking drugs for obstructive airway diseases, many were taking pancreatic enzymes and vitamins, and a majority were taking Pulmozyme®, drugs for acid related disorders, drugs for blood and blood forming organs, antihistamines, and analgesics.

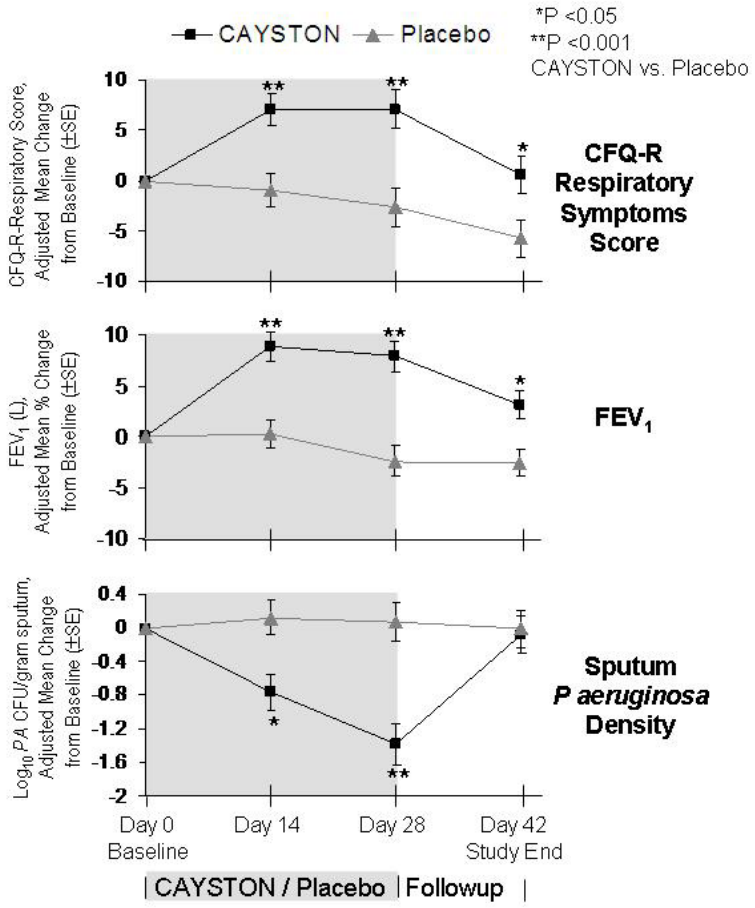
Patient reported outcomes were assessed using the CFQ-R, a validated, disease-specific questionnaire that measures health-related quality of life for children, adolescents, and adults with CF. The instrument encompasses both generic health-related quality of life and CF-specific domains including: Physical Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, Body Image, Eating Disturbances, Treatment Burden, Role/School Functioning, Respiratory Symptoms, Digestive Symptoms, and Weight. The Respiratory Symptoms scale of the CFQ-R asks patients to report on symptoms such as difficulty breathing, coughing, wheezing, colour of sputum, and nature of sputum production. CFQ-R Respiratory Symptoms scores were categorized as improved, stable, or worsened depending on the magnitude and direction of change (change of ≥ 5 points was defined as the minimal clinically important difference).

Study AIR-CF1:
AIR-CF1 enrolled 164 patients with CF and *P. aeruginosa* who were randomized in a 1:1 ratio to receive either inhaled CAYSTON (75 mg) or volume-matched placebo administered 3 times a day for 28 days. Patients were required to have been off antibiotics for at least 28 days before treatment with study drug. The primary efficacy endpoint was improvement in respiratory symptoms as measured by the Respiratory Symptoms scale of the CFQ-R. The mean age was 30 years (range, 7 to 74 years), and the mean baseline FEV_1 % predicted was 55% ±14; 43% were females and 96% were Caucasian. The treatment difference of 9.7 points (p = 0.0005, 95% CI 4.3, 15.1) at Day 28 between CAYSTON-treated and placebo-treated patients for change in CFQ-R Respiratory Symptoms score reflects a clinically significant improvement in respiratory symptoms (see Figure 1).

In the CAYSTON group, 56% of patients showed improvement in respiratory symptoms, versus 37% in the placebo group (p=0.0055) (Table 2). Other CFQ-R domains that demonstrated significant improvement over placebo were Physical Functioning, Emotional Functioning, Health Perceptions, Vitality, and Eating Disturbances.

Pulmonary function, as measured by FEV_1 (L), significantly improved from baseline in patients treated with CAYSTON (see Figure 1). The treatment difference at Day 28 between CAYSTON-treated and placebo-treated patients for percent change in FEV_1 (L) was statistically significant at 10.3% (p<0.0001, 95% CI 6.3, 14.3). The treatment difference at Day 28 between CAYSTON-treated and placebo-treated patients for change in $\log_{10}$ *P. aeruginosa* CFUs in sputum was also statistically significant at -1.45 (p < 0.0001, 95% CI -2.1, -0.8).

Figure 1. Adjusted Mean CFQ-R-Respiratory Symptoms Scores, FEV_1, and *P. aeruginosa* CFUs in Sputum: Change from Baseline to Study End (Days 0-42) (AIR-CF1).



PA: P. aeruginosa

Table 2. Categorized Change in CFQ-R Respiratory Symptoms Scores from Day 0, Child/Teen/Adult Combined: ITT Population (AIR-CF1)

Day 28	Treatment	
	Placebo (N = 84) n (%)	**75 mg CAYSTON[a] (N = 80) n (%)**
Improved	31 (37.3)	45 (56.3)
Stable or no change	15 (18.1)	15 (18.8)
Worsening	37 (44.6)	20 (25.0)
n[b]	83	80
p-value[c]	0.0055	

Improved - increase in score of ≥ 5, Stable or no change - change of less than 5 (increase or decrease), Worsening - decrease in score of ≥ 5.
[a] 3 times a day
[b] number of patients with available data at both timepoints.
[c] Based on the CMH test stratified by baseline response and disease severity. Baseline response was categorized as normal: 75 < CFQ-R, mild to moderate: 50 ≤ CFQ-R ≤ 75, or poor: CFQ-R < 50.

Study AIR-CF2:
AIR-CF2 enrolled and treated 211 patients with CF and *P. aeruginosa*. The primary efficacy endpoint was time to need for inhaled or IV antipseudomonal antibiotics with documented symptom(s) predictive of pulmonary exacerbation. The trial population for AIR-CF2 was more heavily treated than the population for AIR-CF1, as patients must have been treated with ≥ 3 courses of tobramycin inhalation solution (TOBI®) in the preceding year. Patients were permitted to continue taking certain CF treatments such as azithromycin and hypertonic saline regimens during the trial.

The mean age was 26 years (range, 7 to 65 years), and the mean baseline FEV_1 % predicted was 55% ±15; 43% were females and 92% were Caucasian. All patients were treated with TOBI, 300 mg, 2 times a day in the four weeks immediately prior to the 28-day course of CAYSTON or placebo. Patients were randomized in a 2:2:1:1 ratio to receive either inhaled CAYSTON (75 mg) or volume-matched placebo administered either 2 times or 3 times a day for 28 days. Following completion of the 28-day course of CAYSTON or placebo, patients were followed for up to 56 days to assess the need for IV or inhaled antibiotics. The median time to antibiotic need was prolonged by at least 21 days among patients treated with CAYSTON compared to placebo treated patients (CAYSTON, 92 days; placebo, 71 days; p=0.0070).

CAYSTON therapy resulted in significant improvements in the CFQ-R Respiratory Symptoms score, FEV_1(L), and $\log_{10}$ *P. aeruginosa* CFUs in sputum. The treatment difference at Day 28 between CAYSTON- and placebo-treated patients for the change in CFQ-R Respiratory Symptoms score was significantly different at 5.0 points (p = 0.0196, 95% CI 0.8, 9.2). The treatment difference at Day 28 between CAYSTON- and placebo-treated patients for the percent change in FEV_1 (L) was significantly different at 6.3% (p = 0.0012, 95% CI 2.5, 10.1). The treatment difference at Day 28 between CAYSTON-

and placebo-treated patients for the change in log_{10} *P. aeruginosa* CFUs in sputum was significantly different at -0.66 (p = 0.0059, 95% CI -1.1, -0.2).

Repeated Courses
Multiple course, controlled efficacy data are not yet available.

Study AIR-CF3:
AIR-CF3 is an ongoing open-label follow-on study to AIR-CF1 and AIR-CF2, which is evaluating the safety of repeated exposure to CAYSTON and its effect on disease related endpoints for multiple 28-day courses. Patients receive CAYSTON at the same frequency (2 times or 3 times a day) as they took CAYSTON or placebo in the randomized trials. Each 28-day course of CAYSTON is followed by 28 days off CAYSTON.

Over nine 28-day courses of therapy, measures of pulmonary function (FEV_1(L)), 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. A sustained response in these endpoints was seen over multiple courses of therapy (see Table 3). FEV_1(L), the CFQ-R Respiratory Symptoms score, and log_{10} *P. aeruginosa* CFUs showed a dose response over the nine courses, with patients dosed 3 times a day demonstrating greater improvement than those dosed 2 times a day.

Table 3. Mean Change in Disease-Related Endpoints from Baseline Following Initial and Repeated 28-Day Exposures to CAYSTON (75 mg, 3 times a day)

	Change in CFQ-R Respiratory Symptoms Score Mean (SD)	**Percent change in FEV_1 (L) Mean (SD)**	**Change in Log_{10} *P. aeruginosa* CFUs Mean (SD)**
AIR-CF1 (N = 80)	7.88 (18.88)	8.36 (15.23)	-1.48 (2.54)
AIR-CF2 (N = 66)	3.21 (17.65)	3.98 (12.76)	-0.22 (1.69)
AIR-CF3			
CAYSTON Course 1 (N=189)[a]	6.83 (17.38)	7.98 (16.51)	-0.81 (1.76)
Off Treatment	1.34 (15.95)	0.71 (14.51)	-0.28 (1.79)
CAYSTON Course 3 (N=169)[a]	7.34 (18.52)	6.04 (16.49)	-0.53 (2.12)
Off Treatment	3.06 (19.29)	0.72 (15.20)	-0.07 (1.83)
CAYSTON Course 6 (N=135)[a]	5.26 (18.62)	4.78 (17.85)	-0.55 (2.00)
Off Treatment	1.70 (18.61)	-1.43 (15.97)	-0.29 (1.99)
CAYSTON Course 9 (N=124)[a]	6.01 (17.94)	3.98 (17.90)	-0.60 (2.07)
Off Treatment	3.80 (15.41)	-1.05 (17.68)	-0.48 (2.25)

SD = standard deviation
[a]N refers to the number of patients at the start of the course

INDICATIONS

CAYSTON is indicated for control of gram-negative bacteria, particularly *Pseudomonas aeruginosa,* in the respiratory tract of patients with cystic fibrosis.

The primary support for this indication is based on two single 28 day course placebo controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited (see CLINICAL TRIALS).

CONTRAINDICATIONS

Patients with a known allergy to aztreonam or lysine should not take CAYSTON.

PRECAUTIONS

General:
Clinical studies of CAYSTON were performed in patients with stable lung disease. Safety and efficacy have not been demonstrated for CAYSTON in treatment of acute exacerbation of infection. Safety and efficacy have not been demonstrated for patients with FEV_1<25% or >75% predicted, or patients infected with *Burkolderia cepacia.*

Do not use aztreonam *for injection* in the Altera Nebulizer or other nebulizers. Aztreonam *for injection* has not been formulated for inhalation, and contains arginine, a substance known to cause pulmonary inflammation. CAYSTON has been specifically formulated with the amino acid lysine which has been shown to be well tolerated in the airways.

The development of antibiotic-resistant *P. aeruginosa* and superinfection with other pathogens represent potential risks associated with antibiotic therapy. In patients with cystic fibrosis, aztreonam predominately selects for chromosomal mutations leading to beta-lactamase or efflux pump upregulation. This could be associated with cross resistance to other antibiotics including beta-lactams, an important therapy for respiratory exacerbations of cystic fibrosis caused by *P. aeruginosa*. Selection of resistant organisms in treated individuals or their environment could potentially occur. The use of aerosolized antibiotics, including CAYSTON, in the hospital environment should be limited because of the potential for promotion and spread of antimicrobial resistance.

Allergic Reactions: Severe allergic reactions were not observed in clinical trials with CAYSTON. Severe allergic reactions have been reported rarely following administration of aztreonam *for injection* to patients with no known history of exposure to aztreonam. CAYSTON is contraindicated in patients with a known history of aztreonam allergy. If an allergic reaction to CAYSTON does occur, stop administration of the drug and initiate treatment as appropriate.

Patients with a known beta-lactam allergy have received CAYSTON in clinical trials and no severe allergic reactions were reported. However, a history of allergy to beta-lactam antibiotics, such as penicillins, cephalosporins, and/or carbapenams, may be a risk factor, since cross-reactivity may occur. 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.

Bronchospasm: Bronchospasm is a potential complication associated with nebulized therapies. Reduction of ≥15% in FEV_1 immediately following administration of study medication after pretreatment with a bronchodilator was observed in 8% of patients treated with CAYSTON over nine courses of therapy in AIR-CF3.

It is recommended that FEV_1 be measured prior to and after administration of the first dose of CAYSTON, in a setting adequately equipped to deal with a significant fall in FEV_1. Acute falls in FEV_1 immediately following a dose of CAYSTON may require treatment with bronchodilators. Nontransient falls in FEV_1 may require treatment with intravenous anti-pseudomonal drugs and in serious cases, may require hospitalization.

Use in children: Safety and efficacy have not been studied in patients under the age of 6 years. Fifty-five patients under 18 years old received CAYSTON in the placebo-controlled trials and no dose adjustments were made for paediatric patients.

There are limited clinical study data on children 6 to 12 years of age. A total of 18 patients in the 6 to 12 year age group were included in the study of repeated courses of treatment.

Drug Interactions: No formal clinical studies of drug interactions with CAYSTON have been conducted. In clinical studies of CAYSTON, many patients used commonly prescribed CF therapies such as TOBI®, Pulmozyme® (dornase alfa), pancreatic enzymes, oral/inhaled steroids, and/or azithromycin concomitantly with CAYSTON. Single-dose pharmacokinetic drug interaction studies conducted with aztreonam *for injection* and concomitant gentamicin, nafcillin sodium, cephradine, clindamycin, and metronidazole demonstrated no significant interaction.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: 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 tumors. These dose levels represent 7 to 27 times the maximum recommended human dose (MRHD) on a mg/kg basis or 7 to 18 times the MRHD based on plasma C_{max} levels. The only evidence of CAYSTON-related carcinogenicity was a small increase in the incidence of benign C-cell thyroid tumors in female rats at 120 mg/kg/day. There was no such effect at 56 or 31 mg/kg/day.

Genetic toxicology studies performed *in vitro* and *in vivo* with aztreonam *for injection* in several standard laboratory models revealed no evidence of mutagenic potential at the chromosomal or gene level.

Two-generation reproduction studies were conducted with aztreonam *for injection* in rats at daily doses up to 20 times the MRHD. Aztreonam *for injection* before and during gestation and lactation produced no evidence of impaired fertility. The survival rate during the lactation period was slightly reduced in the offspring of rats that received the highest dose. Systemic exposure following CAYSTON in the 75 mg 3 times a day dose is less than 10% of the aztreonam *for injection* recommended dose.

Use in pregnancy**:** *Pregnancy Category B1*
No reproductive toxicology studies have been conducted with CAYSTON. However, studies were conducted with aztreonam *for injection*. Aztreonam has been shown to cross the placenta and enter foetal circulation. No evidence of embryo- or foetotoxicity or teratogenicity has been shown in studies with pregnant rats and rabbits treated with daily doses up to 15 and 5 times, respectively, the human dose of aztreonam *for injection*. In rats receiving 15 times the maximum recommended human dose of aztreonam *for injection* during late gestation and lactation, no drug induced changes in maternal, foetal or neonatal parameters were observed.

Peak plasma concentrations following CAYSTON (75 mg) administration are approximately 90-fold lower than aztreonam *for injection* (500 mg): approximately 0.6 μg/mL compared to 54 μg/mL.

No adequate and well-controlled studies of aztreonam *for injection* or CAYSTON in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, CAYSTON should be used during pregnancy only if the potential benefit outweighs the risk.

Use in lactation: Following administration of aztreonam *for injection*, aztreonam is excreted in human milk at concentrations that are less than one percent of those determined in simultaneously obtained maternal serum.

Information for patients:

Patients should be advised that CAYSTON is for inhalation use only and that it should **only** be administered using the Altera Nebulizer System. Patients should only reconstitute CAYSTON with the provided diluent and should not mix other drugs with CAYSTON in the Altera Nebulizer. Patients should not put aztreonam *for injection* in the Altera Nebulizer.

Patients should be advised to complete the full 28-day course of CAYSTON even if they are feeling better. If a patient misses a dose, they should take all daily doses as long as they are at least 4 hours apart.

Patients taking several medications should be advised to use them in the following order: 1) bronchodilator, 2) chest physiotherapy, 3) other inhaled medications, and 4) CAYSTON.

Patients should be advised to tell their doctor if they have new or worsening symptoms. Patients who believe they are experiencing an allergic reaction to CAYSTON should be told to contact their doctor immediately.

ADVERSE EFFECTS

Clinical Trials Experience

Adverse reactions for CAYSTON were identified from two Phase 3 placebo controlled studies (AIR-CF1 and AIR-CF2) and one Phase 3 open label follow-on study (AIR-CF3) in 306 CF patients with *P. aeruginosa* who were treated with doses of 75 mg of CAYSTON 2 or 3 times a day for 28 days. In the open label study, 238 patients have completed at least three 28-day courses of CAYSTON.

In studies AIR-CF1 and AIR-CF2, 215 CF patients received CAYSTON 75 mg 2 or 3 times a day for 28 days. Table 4 displays adverse reactions reported in >5% of patients treated with CAYSTON (3 times a day or pooled) in Phase 3 placebo-controlled trials.

Table 4 Adverse Reactions Reported in >5% of Patients Treated in the Phase 3 Placebo-Controlled Trials

Event (Preferred Term)	Placebo (N = 160) n (%)	CAYSTON	
		75 mg 3 times a day[a] (N = 146) n (%)	Pooled[b] (N = 215) n (%)
Cough	82 (51%)	79 (54%)	124 (58%)
Nasal congestion	19 (12%)	23 (16%)	39 (18%)
Wheezing	16 (10%)	23 (16%)	32 (15%)
Pharyngolaryngeal pain	17 (11%)	18 (12%)	28 (13%)
Pyrexia	9 (6%)	19 (13%)	25 (12%)
Chest discomfort	10 (6%)	11 (8%)	20 (9%)
Rhinorrhea	10 (6%)	10 (7%)	17 (8%)

[a] Includes patients treated 3 times a day from AIR-CF1 and 3 times a day from AIR-CF2.
[b] Includes patients treated 3 times a day from AIR-CF1 and 2 times or 3 times a day from AIR-CF2.

Additional adverse reactions that occurred in <5% of patients treated with CAYSTON were bronchospasm (3%)[See PRECAUTIONS] and rash (2%).

The following treatment-emergent adverse events occurred at an incidence of ≥ 10% and were determined not to be causally related to CAYSTON: productive cough, respiratory

tract congestion, crackles lung, dyspnoea, and hemoptysis. These events were reported more frequently in the placebo group than in the pooled CAYSTON group.

Adverse events that occurred more frequently with CAYSTON than placebo but which were determined not to be causally related include abdominal pain and vomiting.

Paediatric Population:
Pyrexia was more commonly reported in paediatric than adult patients in the placebo-controlled trials. Pyrexia does not appear to be a manifestation of an allergic reaction.

Treatment beyond three courses (six months):
In study AIR-CF3 166 patients received nine courses (approximately 18 months) of CAYSTON therapy, demonstrating that CAYSTON was well tolerated and no new safety concerns were identified.

DOSAGE AND ADMINISTRATION

The recommended dosage for both adults and paediatric patients 6 years of age and older is one single-use vial (75 mg) administered 3 times a day for a 28-day course (followed by 28 days off CAYSTON therapy). Dosage is not based on weight or adjusted for age. Each dose should be taken at least 4 hours apart.

CAYSTON is administered by inhalation over a 2 to 3 minute period, using the Altera Nebulizer System. CAYSTON should only be used in the Altera Nebulizer. CAYSTON should not be mixed with any other drugs in the Altera Nebulizer. Patients should not put other drugs in the Altera Nebulizer. Patients should use a bronchodilator before each dose of CAYSTON [see CLINICAL TRIALS]. For patients taking several medications, the recommended order is: 1) bronchodilator 2) chest physiotherapy, 3) other inhaled medications, and 4) CAYSTON.

CAYSTON is not for oral, intravenous, subcutaneous, intramuscular, or intrathecal administration.

Use in the elderly: Clinical studies with CAYSTON did not include sufficient numbers of patients aged 65 years old and over to determine whether they responded differently from younger patients. Dosage is not based on weight or adjusted for age.

Use in Patients with Renal Impairment: Aztreonam is known to be excreted renally and therefore administration of CAYSTON in patients with renal impairment should be undertaken with caution.

Placebo-controlled Phase 3 clinical studies with CAYSTON excluded patients with abnormal baseline renal function (defined as creatinine greater than 2 times the upper limit of normal range).

Use in Patients with Hepatic Impairment: Placebo-controlled Phase 3 clinical studies with CAYSTON excluded patients with abnormal baseline hepatic function (defined as aspartate aminotransferase [AST] and alanine aminotransferase [ALT] greater than 5 times the upper limit of normal range).

Instructions for CAYSTON Reconstitution

CAYSTON must be administered immediately after reconstitution. Do not reconstitute CAYSTON until ready to administer a dose.

Take one amber glass vial containing CAYSTON and one diluent ampoule from the carton. To open the glass vial, carefully remove the metal ring by pulling the tab and removing the grey rubber stopper. Twist the tip off the diluent ampoule and squeeze the liquid into the glass vial. Gently swirl the vial until all contents have completely dissolved.

Once reconstituted (one vial and one ampoule), CAYSTON should be administered immediately and only by the Altera Nebulizer System. Like all other nebulized treatments, the amount delivered to the lungs will depend upon patient factors as well as the nebulization system used and its performance. Using the Altera Nebulizer under *in vitro* conditions, the mean inhaled dose (% nominal) was approximately 60 mg (80% of label dose) with a fine particle fraction of approximately 90% as measured by cascade impaction.

Instructions for CAYSTON Administration

Pour the reconstituted CAYSTON into the Altera nebulizer chamber. Turn the unit on. Place the Altera nebulizer handset in your mouth and breathe normally only through your mouth.

Administration typically takes between 2 and 3 minutes. Further instruction for patients on how to administer drug is provided in the Package Insert. Instructions on testing nebulizer functionality and cleaning the handset are provided in the Instructions for Use included with the Altera Nebulizer System.

OVERDOSAGE

No overdoses have been reported with CAYSTON in clinical studies to date. Since the peak plasma concentration of aztreonam following administration of CAYSTON (75 mg) is approximately 0.6 µg/mL, compared to a serum level of 54 µg/mL following administration of aztreonam *for injection* (500 mg), no safety issues associated with CAYSTON overdose are anticipated.

PRESENTATION AND STORAGE CONDITION

Each kit of CAYSTON contains two carton inserts each with a 14-day supply (42 vials of lyophilized CAYSTON packaged in two trays and one tray of 44 diluent ampoules). The four additional diluent ampoules are provided in case of spillage.

A dose of CAYSTON consists of one 2 mL single-use, amber-coloured glass vial of sterile, lyophilized aztreonam (75 mg) and a low density polyethylene ampoule of 1 mL sterile diluent (0.17% w/v sodium chloride). CAYSTON is reconstituted and administered by inhalation using the Altera Nebulizer System.

CAYSTON vials should be stored in a refrigerator (at 2 °C to 8 °C) and not frozen. CAYSTON vials may be stored by patients at room temperature (below 25 °C) for up to 28 days. Diluent ampoules may be refrigerated or stored at room temperature.

Do not use CAYSTON if it has been stored at room temperature for more than 28 days.

CAYSTON should be used immediately upon reconstitution. Do not reconstitute more than one dose at a time.

Do not use diluent or reconstituted CAYSTON if it is cloudy or if there are particles in the solution.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE DRUG: S4

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