# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**050814Orig1s000**

# MEDICAL REVIEW(S)

# CLINICAL REVIEW

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|---|---|
| Application Type | NDA |
| Resubmission Number | 50814 |
| Submission Code | 000 |
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| Letter Date | August 13, 2009 |
| Stamp Date | August 13, 2009 |
| PDUFA Goal Date | February 13 2010 |
| | |
| Reviewer Name | M. Austin Imoisili, MD, MPH |
| Review Completion Date | September 27, 2009 |
| | |
| Established Name | Aztreonam |
| (Proposed) Trade Name | Cayston |
| Therapeutic Class | Monobactam Antibacterial |
| Applicant | Gilead Pharmaceuticals |
| | |
| Priority Designation | Priority Review |
| | |
| Formulation | Inhalational |
| Dosing Regimen | 75 mg TID |
| Indication | Lung Disease in Cystic Fibrosis |
| Intended Population | Cystic Fibrosis Patients |

# BACKGROUND

Gilead Pharmaceuticals, Inc. submitted NDA # 50814 for review as a 505 (b)(2) application to evaluate Aztreonam Lysine for Inhalation (AI) for the improvement in the respiratory signs and symptoms and lung function in Cystic Fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* infection. This submission was received by the Agency in November, 2007. The submission included two pivotal Phase 3 studies 005 and 007. They were randomized, double-blind, placebo-controlled, multicenter studies. A third Phase 3 study (study 006) was an open-label primarily safety and follow-on study which served the dual purpose of being 1.) a follow-up resource for some patients in studies 005 and 007 and 2.) a vehicle to study AI's further safety profile following the receipt of multiple (nine) cycles of AI. It also provided data for the Sponsor to ascertain disease-related outcomes. As alluded to above, eligible patients for this study came from the two randomized studies 005 and 007. While they participated in study 006, they received the AI regimen (BID or TID) corresponding to what they received in the original study whence they came.

The two pivotal Phase 3 studies (005 and 007), the open label Phase 3 study (006) described above, a Phase 2 study (conducted for dose and regimen selection) for Phase 3 studies as well as all the Sponsor's pharmacokinetic (PK) studies were all evaluated during the initial NDA review. On completion of the review, an approvable letter was issued to the Sponsor. A complete response letter from the Agency indicated to the Sponsor that study 007 data had been accepted by the Division as constituting sufficient evidence of efficacy (and safety) of AI, for the indication sought. The review team concluded that study 005 data did not amount to coroborrative evidence to support study 007 data for approval. Therefore, for product approval, the Agency stated that an additional study, in form of a well controlled Phase 3 pivotal trial, would be needed to provide that corroborative evidence in support of study 007 data.

## Reason for Data Re-Analysis and Resubmission by the Sponsor

The Sponsor did not agree with the Division's conclusion. Consequently, they sought hearings from higher authorities in the Office of Antimicrobial Products (OAP)/ Office of New Drugs (OND) by way of dispute resolution. The Sponsor re-analyzed their data to try show why they believe that study 005 results constitute sufficient evidence to support study 007 for the approval of AI.

The company was subsequently advised by Dr. Sandra Kweder to resubmit their re-analysis for a six-month review by the Division.

## The Sponsor's Resubmission

According to the Sponsor, in over six 28-day courses of therapy (alternating with 28-day off-treatment period), a trend toward improvement in each measure was observed while patients were on treatment compared to while off treatment. The Sponsor also reported that a sustained response was observed over multiple courses of therapy; moreover, that clinical improvements were more robust in the TID group than in the BID group. Lastly, they reported that patients who originated from study 007 (receiving TID regimen)

seemed to have demonstrated more improvements in respiratory symptoms, pulmonary function, and sputum *PA* density than did patients from study 005 who received AI/placebo preceded by 28 days of TOBI. Like the other studies, increased cough and productive cough were the major AEs. There was one death in the study but relationship to study drugs could not be established. Hospitalization due to pulmonary exacerbations accounted for most SAEs.

Study 007 was evaluated to establish the efficacy of AI in 80 CF patients who received 75 mg AI TID for 28 days and compared to 84 CF patients who received inhaled volume matched placebo administered TID also for 28 days. All 164 patients constituted the Intent-To-Treat (ITT) population. They served as the primary population for the study. The patients were assessed with a CF Questionnaire-revised (CFQ-R) patient reported outcome (PRO) tool. With this tool, improvement, or otherwise, in clinical symptoms was assessed following completion of treatment on Day 28. This was the primary endpoint. The study met its primary endpoint. A follow up visit at Day 42 was also measured. This, too, was successful. By these results, the study established the efficacy of AI. Study 005 was conducted such that its results, if successsful, would serve to support study 007 results. Like study 007, the treatment was for 28 days. There were two regimens (BID and TID) evaluated in the study. Each regimen had an AI arm and a corresponding placebo arm (i.e. 75 mg AI BID versus Placebo BID; and 75 mg AI TID and placebo TID). The primary endpoint was time to need for an anti-pseudomonal antibiotic. Initiation of AI treatment was preceded by 28 days of TOBI, intended to achieve a fairly comparable lung status at baseline across the different treatment groups. After scientifically evaluating results of study 005, the Medical Officer (MO) had considered the results inadequate to support study 007 data. On that basis, the reviewing MO had recommended an action of approvable for NDA # 50814. The MO had also recommended that the Sponsor conduct another Phase 3 study to corroborate study 007. But there are also other considerations. At this time, there is only one inhalational product (TOBI) approved for the treatment of CF patients. Alternative inhalational products to TOBI are needed for CF patients. If study 007 data had been inadequate, there would be no futher discussion of possible approval of AI. Study 007 data were considered by the Agency to have demonstrated the efficacy of AI for the treatment of CF patients. There were also some acceptable secondary endpoints results (e.g., $FEV_1$ results of AI TID-treated vs placebo TID-treated patients) at least during the earlier periods following the completion of AI treatment by study 005 study patients. These factors and a need for making an alternative inhalational product available for CF patients have allowed the reviewer to consider, entertain or even recommend an approval of AI, despite the other weaknesses in study 005 results. For further elaboration on the basis for recommending AI for approval, see page 34.

## EFFICACY

Efficacy re-analyses of study 005 results were submitted to the Division for review. The safety results of completed study 006 as well as updated safety results of other (newer) aztreonam-related studies were submitted by the sponsor on August 11, 2009.

The efficacy analyses were almost exclusively statistical - analyes of $FEV_1$ measures and the relationship to patient lung improvement, the relationship to the study primary endpoint, and therefore a measure of the efficacy of the product. For more details about the product efficacy re-analyses, see the review done by Drs. Christopher Kadoorie and Thamban Valappil of the statistical team. The safety review is provided in this document.

**SAFETY REVIEW**

An extensive review of the safety of AI was conducted during the initial product evaluation of NDA # 50814. At the end of that review, the safety profile of the product was considered acceptable. The basis of the issuance of an approvable letter by the Agency to the Sponsor had to do with the lack of substantial evidence of product efficacy for approval. The Sponsor's disagreement with the decision, and their subsequent pursuit of a Dispute Resolution with the Agency (for a possible reversal of the decision) led to the current submission of data re-analyses. This resubmitted data included those of the now completed open label study 006, as well as any safety information from completed new or on-going studies since submission of NDA #50814. Given the extensive safety review conducted in NDA #50814, it was determined that data from these studies would be the relevant safety data needed at this time in light of the history of this NDA. Hence, the following Agency's request in the Complete Response letter to the Sponsor:

**When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.**

In response to this request, Gilead has provided the following clinical study reports for review:
1. The final Clinical Study Report for study 006.
2. A safety update for other (new) studies being conducted.

## Study 006

During the NDA review, the study 006 was still on-going. Data submitted from this study were derived from the experiences of patients who had received variable numbers of cycles (each cycle being 28 days) of AI in a scheduled total of 9 cycles. During the NDA review, the interim data were submitted for 125 patients who had received 75 mg of AI TID and for 82 who had received 75 mg AI BID. Completed study 006 now has cumulative data for 189 patients who received 75 mg AI TID and for 85 who received 75 mg AI BID (see table ST1a).

Study 006, of course, had no placebo arm. However, its review was done keeping in mind that AE rates being compared in the BID versus TID arms of study 006 were probably comparable to rates in placebo arms (even sometimes higher in placebo arms) during the review of data derived from the Sponsor's blinded Phase 2 and their pivotal Phase 3 studies submitted for the initial NDA review.

**Safety Table (ST) 1a: Patients who received AI in Study 006**

| | 75 mg BID | 75 mg TID |
|---|---|---|
| **Number of patients for first cycle NDA review** | **n = 82** | **n = 125** |
| **Final study number of patients who participated in study** | **n = 85** | **n = 189** |
| **New Patients** | **n = 3** | **n = 64** |

Safety Table ST1b is a table from the initial NDA review that shows an overview of the number (and %) of patients who received 75 mg AI in study 006 (according to the regimen) who reported at least one adverse event (AE), serious adverse event (SAE), or who died or had their medication discontinued due to an AE or were withdrawn from the study altogether. Table ST 2 is a comparative table submitted following the completion of the study (i.e., after nine cycles of AI treatment).

**ST1b: Study 006 Patients: Overview of Adverse Events (AEs) From NDA Data**

| **Number (%) of patients reporting:** | 75 mg BID N = 82 | 75 mg TID N = 125 |
|---|---|---|
| at least one AE | 45 (54.9) | 68 (54.4) |
| at least one treatment-related AE | 25 (30.5) | 48 (38.4) |
| | | |
| Death | 1 | 1 |
| Death from Study-drug related AE | 0 | 0 |
| | | |
| at least one SAE | 34 (41.5) | 47 (37.6). |
| at least one treatment-related SAE | 4 (4.9) | 6 (4.8) |
| | | |
| AE→ withdrawal from study | 16 (19.5) | 30 (24) |
| Drug-related AE→ withdrawal | 3 (3.7) | 8 (6.4) |
| | | |
| Total Number of AEs | 872 | 1344 |
| → = Leading to or causing | | |

**ST2: Sponsor's Table 18 (Modified): Completed Study 006 – An Overview of AEs**

| Number (%) of patients reporting: | 75 mg BID N= 85 | 75 mg TID N= 189 |
|---|---|---|
| | | |
| at least one AE | 83 (97.6) | 185 (97.9) |
| at least one drug-related AE | 30 (35.3) | 79 (41.8) |
| | | |
| Death | 1 (1.2) | 1 |
| Death from Study-drug related AE | 0 | 0 |
| | | |
| at least one SAE, | 38 (44.7) | 99 (52.4) |
| at least one drug-related SAE | 2 (2.4) | 6 (3.2) |
| | | |
| AE → study drug discontinuation | 7 (8.2) | 38 (20.1) |
| | | |
| Total Number of AEs | 2069 | 5368 |
| Number of drug-related AEs | 137 | 286 |

**SAE= Serious adverse event; % = percent**

***MO comments***

*In comparing the overall frequencies of adverse events from the tables ST1 and ST2, the following picture seems to be apparent:*

*1. as more patients participate, and as they receive more cycles of treatment, the frequencies (percentages) of AEs increase. Hence, those that reported at least one AE rose from percentages in the 50s in table ST1 to the 90s in table ST2, whether in BID or TID arm.*

*2. As patients stayed longer in the study, as reflected particularly in table ST2, the frequencies of AEs reported by AI TID recipients were higher than in the recipients of AI BID regimen.*

*3. A much larger number of study patients reported SAEs in the TID arm in ST2 than in ST1 patients.*

*Of note, however, only 2 (2.4%) BID-treated patients in the later data reported drug-related SAEs compared to 4 (4.9%) who reported treatment-related SAEs in the data submitted earlier.*

## Deaths

There were two deaths in study 006. The first, Patient #152602 (who received AI BID), was discussed in detail on page 90 of the first NDA review. She died after eight courses of AI. Her death was considered unrelated to the receipt of AI.

The second died 6 weeks after receiving the third cycle of AI treatment.
This second patient was a 57-year old Caucasian male, who, as Patient 50651 in study 007, received placebo TID, but as Patient 506651 in Study 006, received 3 courses of AI. His prior medical history included chronic renal impairment, and prior acute and chronic renal failure from Voltaren® therapy. He was hospitalized 3 times while in study 006 as follows:
**First hospitalization** (b) (6) - after his first course of AI, was hospitalized for pulmonary exacerbation, acute worsening of chronic renal failure, and digital artery occlusion. He was subsequently discharged.
**Second hospitalization** (b) (6) **-** was for acute worsening of chronic renal failure for which he began receiving hemodialysis three times weekly. He developed peripheral cyanosis of both hands, associated with decreased sensation in the left middle finger with slow capillary return during this period. He improved.
**Third hospitalization –** (b) (6) was for his second episode of digital artery occlusion, considered secondary to calciphylaxis. He developed worsening ischemia in the digits of three limbs, with patches of gangrene, and intense pain. Cultures of the patient's fingers grew *S. aureus.* As amputation of the affected digits was recommended by the vascular team, the patient made the decision to discontinue dialysis. He subsequently received only palliative care. He was withdrawn from study 006 on November 26, 2007 after the third course of AI. In addition to hemodialysis, non-essential medications, and IV antibiotics also were discontinued. At the patient's request, he was discharged home in (b) (6). The discharge diagnosis was calciphylaxis; end-stage renal failure; and sepsis. He died on (b) (6) (about 6 weeks after the third course of AI) of acute renal failure and concomitant chronic renal failure. The investigator considered this patient's death and all his SAEs unrelated to study drug.

***MO Comments:*** *Establishment of a relationship between this patient's death and the receipt of AI is a difficult case to make. There were comorbidities and concomitant medications. More importantly, he requested to be discharged. Apparently, he asked for a permanent discontinuation of even extraordinary patient-management measures, e.g. dialysis. Apparently also, his doctors respected and followed his wishes. And the man died at home 6 weeks later.*

## Serious Adverse Events (SAEs)

Table ST3 shows the more Common SAEs (≥ 3%) in study 006 from interim data submitted for the NDA review. Table ST4 shows also the more common SAEs (≥3%) in the completed study 006 data that came with re-analysis submission.

**Most Frequently Reported SAEs (≥ 3%) from Study 006 interim data**

| **Table ST3*:*** | **Number (%) reporting SAEs in study 006 – using interim data** | |
|---|---|---|
| **Most Commonly Reported SAEs (Preferred Term)** | **AI 75 mg BID (N = 82)** | **AI 75 mg TID (N = 125)** |
| Cough | 17 (20.7) | 27 (21.6) |
| Productive cough | 11 (13.4) | 14 (11.2) |
| Dyspnoea (including exacerbated /exertional dyspnoea) * | 7 (8.5) | 16 (12.8) |
| Pulmonary function test decreased | 1 (1.2) | 15 (12.0) |
| Haemoptysis | 3 (3.7) | 6 (4.8) |
| Fatigue | 2 (2.4) | 6 (4.8) |
| Abdominal pain (including upper and lower) | 2 (2.4) | 6 (4.8) |
| Pyrexia | 4 (4.9) | 5 (4.0) |
| Respiratory tract congestion | 2 (2.4) | 5 (4.0) |
| Rhinorrhoea | - | 4 (3.2) |
| Exercise tolerance decreased | 3 (3.7) | 4 (3.2) |

**Modified Sponsor's Table 47: Most Frequent (≥ 3%) SAEs from completed study 006**

| **Table ST4** | **Number (%) reporting SAEs in the completed study 006** | |
|---|---|---|
| **Most Commonly Reported SAEs (Preferred Term)** | **AI 75 mg BID (N = 85)** | **AI 75 mg TID (N = 189)** |
| Cough | 20 (23.5) | 58 (30.7) |
| Productive cough | 12 (14.1) | 46 (24.3) |
| Dyspnoea | 11(12.9) | 30 (15.9) |
| Pulmonary function test decreased | 2 (2.4) | 25 (13.2) |
| Exercise tolerance decreased | 6 (7.1) | 19 (10.1) |
| Haemoptysis | 6 (7.1) | 18 (9.5) |
| Respiratory tract congestion | 3 (3.5) | 15 (7.9) |
| Pyrexia | 6 (7.1) | 10 (5.3) |
| Dyspnoea exercerbated | 1 (1.2) | 13 (6.9) |
| Decreased appetite | 3 (3.5) | 11 (5.8) |
| Fatigue | 4 (4.7) | 10(5.3) |
| Abdominal pain | 4 (4.7) | 7 (3.7) |
| Crackles lung | 1 (1.2) | 7 (3.7) |
| Sputum discoloured | 3 (3.5) | 5 (2.6) |
| Chest discomfort | 3 (3.5) | 3 (1.6) |
| Oxygen saturation decreased | 3 (3.5) | 1 (0.5) |

***MO Comments:*** *Table ST3 represents the most commonly reported SAEs in the interim data submitted for the initial NDA review. Table ST4 is derived from completed study data. It is apparent that the types of SAEs are similar. But the higher number of cycles of AI received and the longer the length of period stayed for more cycles of AI, the higher*

*the frequencies of the SAEs reported by study patients. Moreover, there was a tendency to a higher incidence of these SAEs in the AI TID recipients than in the BID arm, perhaps due to the greater exposure to AI.*

## Drug-related SAEs

Table ST5 is displaying the number of study 006 patients with drug-related SAEs as of the time that the study's interim safety data were submitted for the first cycle of NDA review. The SAEs were determined by investigators to be study-drug related. As of that time, only four patients, two in each arm of the study were reported to have these events. Three of them were hospitalized.

Table ST6 tabulates the corresponding events on study completion. At the completion, per the Sponsor, 8 patients altogether (i.e.,2 [2.4%] in the BID group versus 6 (3.2%) in the TID arm) had these events. Some patients had more than one event. Three common drug-related SAEs (cough, productive cough, and dyspnea) were the only drug-related SAEs to occur in more than one patient.
Some of the events led to hospitalization. Per the Sponsor, a common reason for respiratory hospitalization is a decrease in $FEV_1$.

**Reported Drug-related SAEs from Study 006 interim data**

| **Table ST5:** | **Number (%) reporting Drug-related SAEs** | |
|---|---|---|
| **Most Commonly Reported SAEs (Preferred Term)** | **AI 75 mg BID (N = 82)** | **AI 75 mg TID (N = 125)** |
| Arthralgia | 1 (1.2) | - |
| Breath sounds decreased | - | 1 (0.8) |
| Cough | 1 (1.2) | 1 (0.8) |
| Dyspnoea exacerbated | - | 1 (0.8) |
| Joint swelling | 1 (1.2) | - |
| Productive cough | 1 (1.2) | 1 (0.8) |
| Pulmonary function test decreased | - | 1 (0.8) |
| Rash | - | 1 (0.8) |
| | | |

**Modified Sponsor's Table 48: Reported Drug-related SAEs from completed study 006**

| **Table ST6:** | **Number (%) reporting Drug-related SAEs** | |
|---|---|---|
| **Most Reported Drug-related SAEs (Preferred Term)** | **AI 75 mg BID (N = 85)** | **AI 75 mg TID (N = 189)** |
| Cough | 1 (1.2) | 2 (2.1) |
| Productive cough | 1 (1.2) | 2 (2.1) |
| Arthralgia | 1 (1.2) | 0 |
| Joint swelling | 1 (1.2) | 0 |
| Dyspnoea exercerbated | 0 | 3 (1.6) |
| Dyspnoea | 0 | 1 (0.5) |
| Haemoptysis | 0 | 1 (0.5) |
| Wheezing | 0 | 1 (0.5) |

| | | |
|---|---|---|
| Breath sounds decreased | 0 | 1 (0.5) |
| Pulmonary function test decreased | 0 | 1 (0.5) |
| Rash | 0 | 1 (0.5) |
| Lethargy | 0 | 1 (0.5) |
| Multiple occurrences per patient are counted once per system organ class and preferred term. | | |

***MO Comments:*** *At the time the interim data were reviewed for the initial NDA, there were four patients with reported drug-related SAEs. At study completion, the number grew to eight.The most common treatment-related SAEs (TRSAEs) were in the respiratory system. There were two individuals involved in the BID arm whose TRSAEs occurred before the interim data were reviewed and after. More TRSAEs were reported in the TID arm by the end of the study. In general, with most drug products, the longer the time of use or the higher the dose, the more likelihood of developing AEs.In the case of AI, higher dose of AI (given TID) and longer duration of treatment are associated with a greater number of adverse events in the completed study.*

## Discontinuations

**Dropouts and/or Discontinuations in Study 006**

The number and rates of discontinuations in study 006 (interim data) are shown in table ST7. One patient had died at the time data were submitted for the initial NDA review. By study completion, two patients had died. The first and second cases have been discussed in the initial NDA and this review respectively. As shown in table ST7, most rates of dicontinuations in the various categories shown were either comparable in the two regimen arms or were slightly higher in the TID arm. The exceptions were in the "other" row and, during the interim data analysis, the death category (one death at the time). The reasons represented by "other" in study 006 were provided in table S11, page 102, of the previous NDA review.

In the completed study, the relevant discontinuation categories provided by the Sponsor are as shown on table ST8. The categories listed in table ST8 by comparison to the applicable categories in table ST7 indicate higher increases in discontinuation in the TID column. More patients were discontinued among those receiving TID treatments. Altogether, per the Sponsor, 27 patients were discontinued fromthe study due to AEs. Study drug intolerance was evaluated by the investigator at the time of discontinuation. A total of 10 patients discontinued from Study 006 due to study drug intolerance. For those discontinued due to AEs, the AEs were usually different types.

**Dropouts /Discontinuations: Study 006 interim data**

| **Table S T7:** | **Number (%) of Dropouts /Discontinuations Among Study 006 Patients** | |
|---|---|---|
| **Reason for Dropout/Discontinuation** | **75 mg BID** | **75 mg TID** |
| ⇓ **Due to AEs** | **N = 82** | **N =125** |
| Death | 1 (1.2) | - |
| AE Related to study drug/study procedures | 1 (1.2) | 2 (1.6) |
| AE Unrelated to study drug/study procedures | 2 (2.4) | 5 (4.0) |

| | | |
|---|---|---|
| Non-compliance | - | 3 (2.4) |
| Other | 4 (4.9) | 2 (1.6) |
| Personal or administrative reasons | 5 (6.1) | 10 (8.0) |
| Study drug Rx intolerance & documented AE | 2 (2.4) | 5 (4.0) |
| Lost to follow-up | 1 (1.2) | 3 (2.4) |
| | | |

**Modified Sponsor's Table 58: Dropouts /Discontinuations: Completed study 006 interim**

| **Table S T8:** | **Number (%) of Dropouts /Discontinuations in Completed Study 006** | |
|---|---|---|
| **Reason for Dropout/Discontinuation:** | **75 mg BID** | **75 mg TID** |
| ⇓ **Due to AEs** | **N = 85** | **N =189** |
| Death | 1 (1.2) | 1 (0.4) |
| AE Related to study drug/study procedures | 1 (1.2) | 4 (2.1) |
| AE Unrelated to study drug/study procedures | 2 (2.4) | 9 (4.8) |
| Study drug Rx intolerance & documented AE | 2 (2.4) | 8 (4.2) |
| | | |

***MO Comments:*** *The categories of particular interest involved those discontinued due to AEs or drug intolerance. With regards to drug intolerance, there were 8 (4.2%) in the TID arm and 2 (2.4%) in the BID group discontinued because of drug/treatment intolerance. AEs leading to their intolerance of treatment medication, as reported by the investigators at the time of dicontinuation, are summarized in table ST9.*

**Patients with Treatment intolerance in completed study 006**

| **Table ST9:** | | | |
|---|---|---|---|
| **AI TID Group** | **Specific AEs Associated with Intolerance** | **AI BID group** | **Specific AEs Associated with Intolerance** |
| 063604 | Post dose chest tightness; requested to discontinue. | 149602 | $FEV_1$ decreased by28% with the first dose |
| 098605 | $FEV_1$ decreased; chest discomfort; dyspnea; pyrexia, fatigue, | 212602 | Tinnitus (had taken 6 courses of TOBI in the one year prior to participating in study 005 |
| 160607 | Cough | | |
| | | | |
| 212606 | Arthralgia | | |
| | | | |
| 402603 | Hemoptysis, dyspnoea; pulmonary exacerbation in month prior to dosing | | |
| 406602 | Wheezing, dyspnoea, chest wall pain, Cough, tremor, conjunctivitis | | |
| 500662 | Hemoptysis, | | |
| | | | |
| 502606 | Chest discomfort; non-cardiac chest Pain, esophageal pain | | |
| | On-going esophageal pain | | |
| | | | |

## Common Treatment Emergent Adverse Events (TEAEs) - Study 006

Table ST10 summarizes the incidence of the most common treatment-emergent AEs (TEAEs) reported by ≥ 10% of study 006 patients as of the time interim data were gathered and submitted to FDA for the first NDA review. Table ST11 displays the corresponding summary for the completed study 006, for comparison. Cough and productive cough were consistently the most commonly reported AEs. The rest were as listed in the tables in descending order of frequency. The TEAEs written in blue text (productive cough, decreased appetite, and sinus congestion) were reported at rates that were much higher in patients receiving the TID regimen than those receiving the BID regimen. "Pulmonary function test decreased" also was reported at a higher rate in the TID arm but was reported in a smaller number of patients overall. By study completon, additional AEs with higher frequencies in the AI TID arm included asthenia and nausea, the latter involving 13 [15.3%] and 41 [21.7%] patients in the BID and TID arms, respectively.

**Number of Patients (≥ 10 %) Reporting TEAEs in Study 006 interim Data**

| **Table ST10** | **Number (% ) ≥ 10 % of patients reporting TEAEs in study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg BID N = 82** | **75 mg TID N = 125** |
| Cough | 64 (78) | 101 (80.8) |
| Productive cough | 40 (48.8) | 84 (67.2) |
| Respiratory tract congestion | 29 (35.4) | 50 (40.0) |
| Exercise tolerance decreased | 29 (35.4) | 49 (39.2) |
| Pharyngolaryngeal pain | 35 (42.7) | 45 (36.0) |
| Fatigue | 27 (32.9) | 41 (32.8) |
| Decreased appetite | 18 (22.0) | 41 (32.8) |
| Dyspnoea (including exacerbated and exertional Dyspnoea) | 21 (25.6) | 39 (31.2) |
| Pyrexia | 29 (35.4) | 37 (29.6) |
| Nasal congestion | 28 (34.1) | 36 (28.8) |
| Haemoptysis | 20 (24.4) | 27 (21.6) |
| Headache | 18 (22.0) | 25 (20.0) |
| Non-cardiac chest pain | 13 (15.9) | 17 (13.6) |
| Abdominal pain (including upper and lower) | 17 (20.7) | 19 (15.2) |
| Crackles lung | 17 (20.7) | 15 (12.0) |
| Chest discomfort | 15 (18.3) | 20 (16.0) |
| Rhinorrhoea | 15 (18.3) | 27 (21.6) |
| Wheezing | 14 (17.1) | 23 (18.4) |
| Vomiting | 14 (17.1) | 14 (11.2) |
| Nausea | 10 (12.2) | 15 (12.0) |
| Arthralgia | 10 (12.2) | 11 (8.8) |
| Diarrhoea | 9 (11.0) | 12 (9.6) |
| Pulmonary function test decreased | 6 (7.3) | 15 (12.0) |
| Sinus congestion | 6 (7.3) | 20 (16.0) |
| Sinus headache | 7 (8.5) | 14 (11.2) |
| Weight decreased | 12 (14.6) | 11 (8.8) |

***MO Comments:*** *The nature or types of AEs apparently did not change from the time of interim data analysis to the completion of the study. The general increase in the numbers and incidence probably reflects the increased patient population resulting from the additional patients enrolled in the study as well as the longer duration of exposure to treatment until study completion. Cough was predominant AE and therefore the highest in frequency. The AEs in blue and burgundy text had much higher rates of occurrence in the TID group than in the BID arm. All AEs in burgundy text were essentially dyspnea in different descriptions, including "pulmonary function test decreased". Lumped together (in the completed study), 51 (60.0%) patients who received AI BID reported dyspnea versus 173 (91.5%) patients who received TID regimen. That makes a 31.5% difference in frequency rate for patients who received the TID regimen compared to those who received the BID regimen. In the interim analysis, 27 (32.9%) patients who receved AI BID compared to 54 (43.2%) who received TID regimen reported all descriptions of dyspnea. The percentage difference in frequency rates of dyspnea between AI TID and AI BID recepients at this earlier time of the study was only 10.3%.*

**Modified Sponsor's Table 24: Number (≥ 10 %) of TEAEs in Completed Study 006**

| **Table ST11** | **Number (≥ 10 %) of patients reporting TEAEs in study 006** | |
|---|---|---|
| **AEs by Preferred Term** | **75 mg BID** **N = 85** n (%) | **75 mg TID** **N = 189** n (%) |
| Cough | 74 (87.1) | 171 (90.5) |
| Productive cough | 58 (68.2) | 162 (85.7) |
| Exercise tolerance decreased | 43 (50.6) | 111 (58.7) |
| Respiratory tract congestion | 38 (44.7) | 96 (50.8) |
| Pharyngolaryngeal pain | 41 (48.2) | 84 (44.4) |
| Pyrexia | 39 (45.9) | 86 (45.5) |
| Fatigue | 32 (37.6) | 83 (43.9) |
| Decreased appetite** | 26 (30.6) | 86 (45.5) |
| Nasal congestion | 33 (38.8) | 71 (37.6) |
| Dyspnoea | 26 (30.6) | 67 (35.4) |
| Haemoptysis | 26 (30.6) | 66 (34.9) |
| Headache | 27 (31.8) | 61 (32.3) |
| Rhinorrhoea | 23 (27.1) | 62 (32.8) |
| Wheezing | 26 (30.6) | 54 (28.6) |
| Chest discomfort | 21 (24.7) | 46 (24.3) |
| Crackles lung | 27 (31.8) | 38 (20.1) |
| Pulmonary function test decreased | 12 (14.1) | 50 (26.5) |
| Vomiting | 20 (23.5) | 41 (21.7) |
| Nausea | 13 (15.3) | 41 (21.7) |
| Non-cardiac chest pain | 18 (21.2) | 36 (19.0) |
| Sinus congestion | 10 (11.8) | 41 (21.7) |
| Weight decreased | 14 (16.5) | 28 (14.8) |
| Diarrhoea | 10 (11.8) | 31 (16.4) |
| Sinus headache | 9 (10.6) | 30 (15.9) |
| Arthralgia | 12 (14.1) | 25 (13.2) |
| Back pain | 13 (15.3) | 24 (12.7) |

| | | |
|---|---|---|
| Dyspnoea exacerbated | 6 (7.1) | 31 (16.4) |
| Abdominal pain | 25 (29.4) | 45 (23.8) |
| Dyspnoea exertional | 7 (8.2) | 25 (13.2) |
| Asthenia | 5 (5.9) | 26 (13.8) |
| Constipation | 9 (10.6) | 19 (10.1) |
| | | |

**Treatment-Related AEs (TEAEs) for Study 006 Interim Data**

A summary of treatment-related AEs (TRAEs) occurring in study 006 with incidence rates in any study regimen ≥ 3% is presented for the interim data in Table ST12 and for the completed study 006 in table ST13. For the interim data, TRAEs for rates ≥ 3% are almost exclusively in the respiratory system, including cough, hemoptysis, dyspnoea, etc. In the complete study 006, all TRAEs with incidence rates in any study arm ≥ 3% (except headache and arthralgia) were also in the respiratory system. Thus the completed study is generally similar to the previous review with respect to TRAE safety profile. The most common TRAE at study completion was cough (BID group [20.0%] and TID group [21.2%]).

**The Most Common (≥ 3% of Patients) TRAEs in Study 006 interim Data**

| **Table ST12** | **Number (%) of patients reporting TRAEs in study 006 interim analysis** | |
|---|---|---|
| | **75 mg BID** | **75 mg TID** |
| **AEs preferred term** | **N = 82** | **N =125** |
| Cough | 14 (17.1) | 22 (17.6) |
| Haemoptysis | 7 (8.5) | 8 (6.4) |
| Dyspnoea | 2 (2.4) | 7 (5.6) |
| Chest discomfort | 4 (4.9) | 6 (4.8) |
| Respiratory tract congestion | - | 6 (4.8) |
| Productive cough | 3 (3.7) | 5 (4.0) |
| | | |

**Modified Sponsor's Table 41: The Most Common (≥ 3%) TRAEs in Completed study 006**

| **Table ST13** | **Number (%) of patients reporting TRAEs in completed study 006** | |
|---|---|---|
| | **75 mg BID** | **75 mg TID** |
| **AEs preferred term** | **N = 85** | **N =189** |
| Cough | 17 (20.0) | 40 (21.2) |
| Dyspnoea (including exertional and exacerbated) | 2 (2.4) | 14 (7.4) |
| Haemoptysis | 8 (9.4) | 13 (6.9) |
| Pharyngolaryngeal pain | 6 (7.1) | 8 (4.2) |
| Productive cough | 3 (3.5) | 11 (5.8) |
| Chest discomfort | 4 (4.7) | 10 (5.3) |
| Headache | 4 (4.7) | 5 (2.6) |
| Nasal congestion | 4 (4.7) | 3 (1.6) |
| Respiratory tract congestion | 1 (1.2) | 7 (3.7) |
| Arthralgia | 3 (3.5) | 6 (3.2) |
| | | |

***MO's Comment:*** *The TRAE profile in the completed study is generally similar to that of the interim data analyzed during the initial NDA review. The slightly higher rates of TRAEs may be due to the disproportionately higher number enrolled in the TID arm (compared to BID arm which enrolled only 2 new patients since interim data were submitted) and more exposure to AI TID regimen multiplied by the additional number of cycles.*

## Vital Signs

No drug- or treatment-related vital sign AE of significance was reported in the completed study 006 or the interim study results.

**Heart Rate**

Overall, only one patient was reported to have increased heart rate that was considered drug-related. All other events were considered unrelated to study drug. Two patients in BID arm had cardiac arrythmias. Patient 123601 had moderate flutter considered unrelated to study drug. Patient152603 reported mild palpitations on two occasions, one of which was considered by the investigator to be possibly related to study drug, despite a history of previous palpitations felt by the patient to be stress-related. In the TID arm, patients 406601 and 013601 reported palpitations that were considered mild and moderate respectively. Only that of patient 406601 was considered study-drug related.

**Blood Pressure**

Mild hypertension was reported for patients 004605 (TID), 013609 (TID), 406601 (TID) and 027603 (BID), moderate hypertension was reported in Patients 170601 (TID) and 403601 (BID), and severe hypertension was reported in Patient 401602 (BID) . According to the Sponsor, no case of hypertension was considered related to study treatment.

**Temperature**

Per the Sponsor, there were no significant differences between the BID and TID groups in mean changes from baseline in body temperature in the completed study 006 results. Pyrexia was reported in 39/85 (45.9%) patients who received BID regimen compared to 86/189 (45.5%) who received AI TID. In the interim data, 29/82 (35.4%) patients treated with the BID regimen reported fever as an AE compared to 37/125 (29.6%) who received the TID regimen. The differences in pyrexia incidence between the interim and the completed study results probably had to do with more people receiving the drug for a longer period of time. The Sponsor noted that pyrexia was reported more frequently among pediatric patients <18 years of age than older patients ≥ 18 years of age [30 (54.5%) vs. 95 (43.4%), respectively].

Four patients reported pyrexia considered by the investigator to be drug-related and were assigned the following pyrexia severity scores: patient 118601 (BID arm) moderate; patient 152602 (BID arm) mild; patient 098605 (TID arm) mild; and patient 500603 (TID arm) moderate.

**Respiratory Rate**
There were no differences between the BID and TID groups in median changes in respiratory rate in the completed study 006 results. Per the Sponsor, there were no clinically significant changes in the median respiratory rate from Visit 1 (baseline) for the BID group and the TID group.

**Airway Reactivity**
Airway reactivity (percent change from pre-treatment to 30 minutes after treatment in $FEV_1$ [L]) was assessed at all study 006 visits for Treatment Courses 1 through 9. Per the Sponsor, mean percent change in $FEV_1$ was similar between the BID and TID groups and did not decrease (worsen) with repeated courses of AZLI.

***MO Comments:*** *There were no vital sign abnormalities that were of significant concern in the completed study 006 results. In the interim data, aside from the incidence of low pulse rate which was slightly higher in the TID arm compared to the BID arm, all other frequency rates were similar and no regimen effect on vital signs was apparent.*

## Clinical Laboratory Evaluation

**Hematology Shifts from Baseline**
Table ST14 shows the number (and percentages) of patients in study 006 from the data submitted for the initial NDA review. Table ST15 represents the number (and percentages) of the patients following the completion of the study. These were patients whose shifts in their laboratory values (below or above normal range) occurred following the receipt of study treatment until completion of (or exit from) the study. For table ST15, The numbers of patients assessed (n) for the hematologic values of interest are indicated under the applicable hematologic indices.

**Leukocytosis and Leukopenia**
The upper limit of WBC used in previous NDA review was 11 x $10^3/mm^3$. Values above were considered leukocytosis. Values below 4.0 x $10^3$ were considered leukopenia. As indicated in previous review, the elevated WBCs probably represented acute inflammatory changes related to underlying CF chronic lung disease.
For the completed study 006, 11/78 (14.1%) versus 23/177 (12.9%) were reported to have leukocytosis in the AI BID-treated versus AI TID-treated patients respectively. These rates were comparable across the regimen groups as well as to interim data groups in table ST14.
The numbers reporting leukopenias are shown in both tables ST14 and ST15 and were small.

**Eosinophilia**
Eosinophilia was reported twice in table 63. The rates of eosinophilia were higher in the interim data analysis (although the corresponding regimen arms were comparable) than in the completed study results.

**Anemia**

The incidence of anemia was higher in the TID arm (compared to the BID arm) in the data submitted for the initial NDA review. In the completed study, the incidence in the TID arm was lower than the rate in the prior analysis.

**Pancytopenia**

Pancytopenia was not reported.

**Hematology Findings in Study 006 Patients in Study 006 interim Data**

| **Table ST14** | **Number (%) of patients with hematologic abnormalities in Study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg BID N = 82** | **75 mg TID N = 125** |
| | | |
| **Leukocytosis (WBC >11 x $10^3$)** | | |
| Normal BL: Increase on treatment | 11 (13.4) | 17 (13.6) |
| High BL: Increase on treatment | 3 (3.7) | 8 (6.4) |
| Combined | 14 (17.1) | 25 (20.0) |
| | | |
| | | |
| **Leukopenia (WBC <4.0 x $10^3$)** | | |
| Normal BL: Decrease on treatment | 1 (1.2) | 2 (1.6) |
| | | |
| **Eosinophilia** | | |
| Normal BL: Increase on treatment | 6 (7.3) | 9 (7.2) |
| | | |
| **Anemia (HCT < 35)** | | |
| Normal BL: Decrease on treatment | 1 (1.2) | 9 (7.2) |
| | | |
| **Thrombocytopenia (Plt count < $10^5$/mL)** | - | - |
| Normal BL: Decrease on treatment | | |
| | | |
| **Pancytopenia** | - | - |
| Plt = Platelet; BL = baseline | | |

***MO Comments:***

*Some of the hematology shifts in numbers (and percentages) presented in the completed study table (ST15) are smaller than those reported in the corresponding hamatology parameter being compared in the interim data in table ST14. That would seem counterintuitive. The reasons are as follows:*

***1.*** *The completed study table compared shifts in parameter values from the baseline visit to the last study visit; whereas the interim data included reports (in the initial submission) of changes occurring at any point during treatment.*

*2. The availability of dataset during the initial NDA review allowed ascertainment of shifts not only from normal baseline values but also changes from abnormal baseline values. In the completed study, the reviewer utilized the Sponsor's data presented in their final Clinical Study Report, as the Sponsor had provided no dataset at the time of review.*

*The regimen-related incidence of anemia that was apparent in the interim data (showing higher anemia incidence in AI TID group) did not appear to persist by study completion. In the interim data analysis, the eosinophilia rates in the two study arms were comparable. Eosinophilia reported in the completed study showed four AI TID-treated patients (2.3%) compared to none in the BID arm, after nine cycles of AI, – suggesting, perhaps, that all eosinophilia reported in the patients who received BID regimen prior to interim data analysis, and a smaller number in the TID arm had resolved by study completion. Otherwise, there appeared to be no other significant differences in regimen with regards to hematologic parameters at the completion of study 006.*

**Modified Sponsor's Table 63: Hematology Shifts from Baseline to Last Visit**

| **Table ST15** | **Number (%) of patients with hematologic abnormalities in Study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg BID N = 85** | **75 mg TID N = 189** |
| | | |
| **Leukocytosis** | | |
| N | 78 | 178 |
| Became high while on treatment | 11 (14.1) | 23 (12.9) |
| | | |
| **Leukopenia** | | |
| N | 78 | 178 |
| Became high while on treatment | 3 (3.8) | 2 (1.1) |
| | | |
| **Neutrophils** | | |
| N | 78 | 177 |
| Became high while on treatment | 11 (14.1) | 28 (15.8) |
| Decrease on treatment | 2 (2.6) | 1 ( 0.6) |
| | | |
| **Eosinophilia** | | |
| **N** | 78 | 177 |
| Normal BL: Became high on treatment | 0 (0.0) | 4 (2.3) |
| | | |
| **Anemia** | | |
| N | 78 | 178 |
| Decrease on treatment (using hematocrit numbers) | 3 (3.8) | 3 (1.7) |
| | | |
| **Thrombocytopenia** | | |
| N | 78 | 178 |
| Decrease on treatment | 1 (1.3) | 1 (0.6) |
| | | |
| **Pancytopenia** | NR | NR |

WBC = white blood cells; NR = None reported

## Serum Chemistry Changes

Table ST16 displays the number (and percent) of patients with chemistry abnormalities as analyzed in the interim study 006 data in the first NDA review cycle. Dataset of the interim study results submitted at that time allowed asertainment of various laboratory result changes, degrees of change and the patients involved. Table ST16 contents were discussed in the initial NDA review.
At the time of writing this re-analysis safety review of complete study 006 results, the corresponding dataset (which did not accompany the resubmission) has still not been made available although requested from the Sponsor. Therefore, the reviewer has relied on the Sponsor's case study report for completed study results. In table ST17, therefore, patients with abnormal results have been presented in terms of the number (and percent) of patients with high or low chemistry abnormalities, but without addressing how far beyond the limits of normal these values are.

In table ST17, the number (and percent) of patients with reported abnormalities are presented for the hepato-renal systems as well glucose and potassium. Other chemistry indices not reported either showed small or no reported abnormalities. For those shown in the table (i.e., ST17), liver enzyme abnormalities were comparable in the regimen arms and appeared lower in numbers and percentages than during the interim data analysis. This comparison depended on parameters used as the margins of abnormality used by the Sponsor in the completed study to determine their high or low values. In table ST 16, most liver enzyme abnormalities were < 3 times upper limit of normal (ULN) in values with very small numbers of outliers. There were no Hy's law cases.

Blood urea nitrogen and creatinine abnormalities occurred in a small number of patients in the completed study, as determined by the Sponsor; the numbers were smaller than the the abnormal cases during the interim analysis.

Hyper- and hypo-glycemia were comperable in both regimen arms. They were difficult to compare with interim data as the latter comparison was done by relating laboratory values to *upper limit of normal* (ULN) measure.

The incidence of high potassium was higher on the AI TID arm than in BID arm, involving 6 (3.3%) people in the TID arm compared to none in the BID arm.

## Number (%) of patients with chemistry abnormalities in Study 006 (Interim Data)

| **Table ST16** | **Number (%) of patients with chemistry abnormalities in Study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg BID N = 82** | **75 mg TID N = 125** |
| **ALT** | | |
| ↑ from normal BL <3x | 19 (23.2) | 23 (18.4) |
| ↑ from normal BL >3x - 5x ULN | - | 1 (0.8) |
| ↑ from normal BL >5x – 10x ULN | 1 (1.2) | - |
| ↑ from normal BL >10x - 20x ULN | - | 1 (0.8) |
| | | |
| **AST** | | |
| ↑ from normal BL <3x | 11 (13.4) | 16 (12.8) |
| ↑ from normal BL >3x - 5x ULN | | |
| ↑ from normal BL >5x – 10x ULN | - | 1 (0.8) |
| ↑ from normal BL >10x - 20x ULN | - | 1 (0.8) |
| | | |
| **Total Bili** | | |
| Rise from normal baseline levels to > 1.5 x ULN | - | 1 (0.8) |
| Rise from normal baseline levels to < 1.5 x ULN | 7 (8.5) | 5 (4.0) |
| | | |
| **Clinically significant GGT ↑** | | |
| ↑ from Baseline | 21 (25.6) | 22 (17.6) |
| | | |
| **Hy's Law** | - | - |
| | | |
| **Blood Urea Nitrogen (BUN)** | | |
| Increase from normal baseline | 8 (9.8) | 8 (6.4) |
| | | |
| **Creatinine** | | |
| Rise from normal or elevated BL level | 10 (12.2) | 13 (10.4) |
| | | |
| **Hyperglycemia** | | |
| ↑ but < 3x ULN from normal baseline | 38 (46.3) | 51 (40.8) |
| >3x-5x ULN - ↑ from normal BL | 3 (3.7) | 3 (2.4) |
| | | |

| | | |
|---|---|---|
| **Hypoglycemia** | | |
| Serum glucose ≥ 40 but < 50 (mg/dL) | 4 (4.9) | 5 (4.0) |
| Serum glucose < 40 | - | 1 (0.8) |
| | | |
| BL = Baseline; ↑ = increase; ULN = Upper limit of normal; U = units of glucose level = mg/dL; № = number; lab. = laboratory; Bili = Bilirubin; - = None present or no value provided. | | |

**Modified Sponsor's Table 63: Chemistry Shifts from Baseline to Last Visit (completed study 006)**

| **Table ST17** | **Number (%) of patients with chemistry abnormalities in Study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg BID N = 85** | **75 mg TID N =189** |
| **ALT** | | |
| n | 82 | 182 |
| Became high while on treatment | 9 (11.0) | 21 (11.5) |
| | | |
| **AST** | | |
| n | 81 | 181 |
| Became high while on treatment | 6 (7.4) | 16 (8.8) |
| | | |
| **Total Bilirubin** | | |
| n | 82 | 182 |
| Became high while on treatment | 4 (4.9) | 5 (2.7) |
| | | |
| **GGT** | | |
| n | | |
| Became high while on treatment | 1 (1.2) | 4 (2.2) |
| | | |
| **Serum potassium (mEq/L)** | | |
| n | 81 | 182 |
| High | - | 6 (3.3) |
| Low | - | 1 (0.5) |
| | | |
| **Blood Urea Nitrogen (BUN)** | | |
| n | | |
| Became high while on treatment | 3 (3.7) | 3 (1.6) |
| | | |
| **Creatinine** | | |
| n | | |
| Became high while on treatment | 2 (2.4) | 2 (1.1) |
| | | |
| **Hyperglycemia** | | |

| | | |
|---|---|---|
| n | | |
| Became high while on treatment | 13 (15.9) | 32 (17.6) |
| | | |
| **Hypoglycemia** | | |
| n | | |
| Became low while on treatment | 2 (2.4) | 10 (5.5) |
| - = None reported. | | |

***MO Comments:***
*The various numbers of patients reporting chemistry AEs in the interim data (table ST 16) exceed those in the completed study data (tableST 17). The reasons provided to explain this apparently counter-intuitive occurrence for patients reporting hematology AEs previously desribed are also applicable chemistry laboratory abnormal results. Part of the reasons had to do with the fact that the Sponsor reported only the comparison of baseline to last visit laboratory values in the final report, whereas the interim report involved all patients with changes in abnormal laboratory values at any time during the study.*
*Regimen-related chemistry abnormalities did not appear to be an issue overall among study 006 patients as shown in the tables above. Cases of ALT/AST elevation were comparable across regimen arms. No Hy's law cases were reported.*
*The hyperglycemia involving some of the many cases reported in the interim data gathered for for use in the initial NDA review, apparently had resolved by study completion.*
*Hypoglycemia patients and rates were higher in the TID arm than in the BID arm in the completed study results. Overall, however, the numbers were small.*

## Clinical Microbiology (summarized)

Pathogens isolated from study patients included *Pseudomonas aeruginosa* (*PA*), *Burkholderia cepacia complex* (BCC), *S. aureus (MSSA and MRSA), Stenotrophomonas maltophilia, A. xylosoxidans, Aspergillus* spp. or *Candida* spp.

***Pseudomonas aeruginosa* (*PA*)**

Overall, *PA* was isolated from 94.8% of 269 patients who had available data at baseline (Visit 1). The percentages were similar for the BID and TID groups (94.0 versus 95.1%) respectively. The degree of presence or absence of *PA* probably depended upon variations in sampling. The Sponsor stated that eradication of established *PA* infection could not be expected for suppressive therapy.

**Group MIC**
Per the Sponsor, the $MIC_{50}$ of aztreonam for all *PA* isolates at baseline was 4 μg/mL in both BID and TID patients; the $MIC_{90}$ was 128 μg/mL for BID and TID subgroups.

For the BID subgroup, the $MIC_{50}$ increased from 4 μg/mL to 16 μg/mL after the initial 3 cycles of AI treatment. This remained unchanged for several visits. Beyond 9 cycles, the $MIC_{50}$ returned to the baseline value of 4 μg/mL. In the BID group also, the $MIC_{90}$ increased from128 μg/mL to 512 μg/mL and remained unchanged until a return to baseline of 128 μg/mL after 9 cycles.

In the TID group, the $MIC_{50}$ remained unchanged from baseline. The $MIC_{90}$ increased from baseline to 512 μg/mL after the 4th treatment cycle and and remained up to the 9th cycle. It subsequently returned to baseline (128 μg/mL) after the 9th cycle.

**Highest individual MIC**

Per the Sponsor, the $MIC_{50}$ of aztreonam for the *PA* isolates with the highest MIC was 8 μg/mL at baseline for BID and TID subgroups. The corresponding $MIC_{90}$ of aztreonam for the *PA* isolate with the highest MIC at baseline for BID was 128 μg/mL and for TID was 256 μg/mL.

In the BID group, the $MIC_{90}$ for the *PA* isolate with the highest MIC from each patient increased up to 1024 μg/mL through the 8th cycle, but returned to the baseline post the 9th cycle visit (visit 20). In the TID group, the $MIC_{90}$ increased intermittently from cycles 6 through 9 and returned to within 2-fold change of the baseline value at Visit 20.

**MICs of other Antibiotics for *PA***

With regards to MICs of other antibiotics for *PA,* the Sponsor reported the following: "Apart from transient changes, there were no notable increases in the $MIC_{50}$ or $MIC_{90}$ of any of the other antibiotics tested against *PA* (amikacin, cefepime, ceftazidime, ciprofloxacin, gentamicin, meropenem, piperacillin, tobramycin, and ticarcillin/clavulanate) after treatment with AZLI. However, there were notable decreases in the $MIC_{90}$ of tobramycin for all *PA* isolates tested and *PA* isolates with the highest MICs. While all $MIC_{50}$ data remained unchanged for tobramycin, persistent decreases in the $MIC_{90}$ were observed in the BID group for all *PA* isolates tested and *PA* isolates with the highest MIC. In the TID group, decreases in the $MIC_{90}$ of tobramycin were persistent for all *PA* isolates tested and transient for the *PA* isolates with the highest MICs"

***Burkholderia cepacia* Complex**

Per the Sponsor, *B.cepacia* complex (BCC) was not present in any AI BID-treated patients at baseline and did not appear in this treatment group during the study. BCC was however present in one AI TID-treated patient at baseline. Treatment-emergent intermittent isolation of BCC occurred in 4 additional patients in the course of the study 006. The narratives for all five patients are as follows:

- **Patient 019601:** The sputum sample at baseline tested positive for BCC. This patient continued the study through the second treatment course and then was withdrawn. Sputum samples at Visits 2, 3 and at early termination visit were negative, positive and positive, respectively for BCC. This patient entered this study after completing study 007 where he had been randomized to receive AI TID. The patient had tested negative for BCC at all timepoints in study 007.

• **Patient 019602:** The sputum samples through two AI cycles (Visit 1-4) tested negative for BCC. Sputum samples through the third cycle (Visits 5 and 6) tested positive for BCC. This patient continued in the study through the fifth treatment course and then was withdrawn. Sputum samples from Visits 8, 9, 10 (up to treatment course 5) and at early termination, tested negative for BCC.

• **Patient 104608:** The patient was withdrawn from the previous study, study 005, at Day 28 after testing positive for BCC. He was subsequently enrolled in study 006 and was withdrawn for noncompliance with study visits and study procedures. His sputum culture from the early termination visit (after the second treatment course) tested positive for BCC.

• **Patient 152611:** The sputum sample from Visit 10 (off 4 courses) tested positive for BCC. No other sputum samples tested positive throughout the study and the patient completed the entire study.

• **Patient 160603:** Sputum samples from third treatment course till the end (Visits 5, 12, 14, and 20) tested positive for BCC. Sputum samples for previous visits tested negative for this pathogen and the patient continued in the study. The patient entered this study after completing Study study 007 where he had been randomized to receive AI TID. His test results from the Screening visit of study 007 were positive for BCC. All subsequent tests for BCC in study 007 were negative.

**MSSA and MRSA**

Aztreonam typically provides coverage exclusively for Gram-negtive bacteria. There is a theoretical concern that AZLI therapy in patients with CF could provide a growth advantage for MSSA and MRSA (being Gram-positive) over that of *PA* in the lung. For this concern, the Sponsor reports that *S. aureus* was regularly cultured for over nine courses of AZLI treatment. MRSA was identified by growing cultured *S. aureus* using the cefoxitin disk diffusion method. At baseline (Visit 1), culture data were available for 269 patients. Of these 269 patients, 98 (36.4%) tested positive for *S.aureus*. Of these 98 patients, the presence of a MSSA or MRSA infection was determined in 90/98 (91.8%) patients. Overall, 23.5% of the patient population at baseline (Visit 1) in the study was culture positive for MSSA while 13.0% of the patient population was culture positive for MRSA.

Of the 84 BID-treated patients with culture data, 33 (39.3%) patients tested positive for *S. aureus*. Of the 185 TID-treated patients with culture data, 65 (35%) patients tested positive for *S. aureus.*

Following nine courses of AI BID therapy, the percentage of patients with MSSA was 22.2% - lower than that of Visit 1 (31.0%). The percentage of patients with MRSA increased from 8.3% at Visit 1 to 11.1% at after 9 corses of AI.

Following nine courses of AI TID therapy, the percentage of patients with MSSA was 26.1% - higher than that of Visit 1 (19.7%). The percentages of patients with MRSA were 15.4% and 16.0% at Visits 1 and 19 (after 9 courses of AI), respectively.

***MO comments***
*For Pseudomonas aeruginosa* (*PA*), *although the general initial increase in MIC on treatment seems to return to baseline at the the end of treatment, the potential for MIC creep following years of product use, were it approved, is still unclear. For Burkholderia cepacia complex, wether the product slows, accelerates or indifferent with regards to the rate of emergence of BCC based on the data presented by the Sponsor is difficult to ascertain. Given the non-susceptibility of Gram-positive organisms to Aztreonam, its impact on MSSA (particularly MRSA) growth changes in the lungs of CF patient is uncertain despite the slight increase in MRSA at the end of treatment compared to baseline in study 006 particularly in the TID arm. The increase was slight after 18 months of alternate month treatment.*

## Study 006 Safety Conclusions

Study 006 was an open-label follow-on study for patients enrolled from studies 005 and 007. It consisted of AI BID and AI TID arms, in accordance with the regimen patients received in their study of origin (i.e. study 005 or 007). The interim safety data consisted of 82 patients who received AI BID and 125 who recived AI TID. These data were reviewed in the original NDA. By study completion, 85 patients altogether had received AI BID, and 189, AI TID. During the initial review, patients were at different stages of a nine-cycle schedule of AI treatment. The current review has evaluated the completed study results comprising the cumulative data of all from whom the initial interim data were derived as well as the additional patients who received the product since then (regardless of the number of cycles received) up to the end of the study. According to the Sponsor, 84.7% of patients who received BID regimen and 82.0% in the TID group received at least 80% of the planned doses while on treatment. Rates of AEs or laboratory abnormalities were compared between AI BID and AI TID study arms as well as to the findings in the NDA review to ascertain possible occurrence of new AEs or laboratory abnormalities. This was done keeping in mind that these rates were comparable to rates in placebo arms (even sometimes higher in placebo arms) during Phase 2 and pivotal Phase 3 study during the NDA review process.
After reviewing the completed study 006 safety results, and comparing with prior review of study 006 in the original NDA, the reviewer has come to the following conclusions:

1. Two deaths were reported in study 006. One involved a 44-year old female who had received eight courses of AI BID in this open-label study. She had multiple disease complications and multiple surgical procedures. No causal relationship could be established between her receipt of AI and her death. The second patient was a 57-year old male who had received 3 cycles of AI TID. He had end-stage renal disease. He requested i) a discontinuation of his renal dialysis and, subsequently, ii) his discharge from the hospital altogether. He died at home six

weeks later. A relationship between the receipt of AI and his death could not be established.

2. The rates of serious adverse events (SAEs) were generally higher in the TID arm than in BID arm of the study. The three most common SAEs were cough, productive cough and dyspnea. There appeared to be a relationship between SAE incidence and length of time (or number of cycles) that patients received AI, particulaly the TID regimen. It is apparent also that the types of SAEs were similar in the interim versus the completed study. But the higher number of cycles of AI received and the greater length of time stayed for more cycles of AI, the higher the frequencies (seemingly) of the SAEs reported by study patients. Greater exposure to AI could have been a factor.

3. The number of treatment-related SAEs was small. Four patients reported such SAEs from study 006 in the interim data submitted for the initial NDA review. At completion eight patients reported such AEs. They were mostly pulmonary-related SAEs. Of these, 2 (2.4%) patients received AI BID while 6 (3.2%) received AI TID. The most common were cough, productive cough and dypsnea although the numbers were small.

4. The rates of discontinuaton were generally low but still higher in the TID arm than in the BID arm. Similar categories of reasons for discontinution were slightly higher in the completed study (mainly in TID arm) than in the interim data. For drug intolerance in the completed study, there were 2 (2.4%) in the BID group versus 8 (4.2%) in the TID arm that were discontinued because of drug/treatment intolerance. The rate was slightly higher in the TID arm in the completed study than in the interim data. This was also the case in the rates of discontinuation but the numbers were small.

5. Types of AEs did not change from the time of interim data analysis to the completion of the study. Cough, productive cough, decreased exercise tolerance and respiratory tract congestion were the four most common AEs as of the time of interim data collection as well as at study completion. The rates were higher when the study was completed than at time interim data were gathered. The TID arm patients had higher frequencies of occurrence than in the BID arm.

6. Cough, dyspnea, and hemoptysis were the three most frequently reported treatment-related AEs in both in the interim data and in the completed study result. In general, AEs occurred either at comparable rates in both study arms or or slightly higher in the TID arm. There were no new AEs not previously seen at the time interim data were gathered for the initial NDA review.

**Vital Signs**

7. Overall, no drug- or treatment-related vital sign AE of significance was reported in the completed study 006. The few vital sign-related AEs were mild and did not seem clinically significant.

**Laboratory Data**

8. Aside from eosinophilia [involving 4 (2.3%) patients in the TID arm versus none in the TID arm], the other hematologic indices occurred at comparable and low rates across study arms.

9. Aside from hyperkalemia which was reported in 6 (3.3%) of patents who reveived AI TID treatment versus none in the AI BID arm, all other serum chemistry value abnormalities (ALT, AST, total bilirubin, serum glucose abnormalities, etc) were reported at generally comparable rates among patients who received AI BID and AI TID study patients in the completed study.

**Microbiology**

10. As patients received multiple courses of AI, the MICs of *Pseudomonas aeruginosa* generally trended upward initially, came to a "plateau", and generally returned to baseline after the last cycle.

11. The sputum sample at baseline tested positive for *Burkholderia cepacia* complex (BCC) for one patient at baseline. The sputum sample for four additional patients tested positive during the course of study 006.

12. A slight increase in MRSA at the end of treatment (compared to baseline), more in the TID arm than in the BID arm, was reported. Its long term implication, if the product were approved, is unclear.

**Overall Conclusion of Safety Review of Completed Study 006**

The initial review of NDA 50-814 revealed no safety findings that constituted a barrier to the approval of AI for use in CF patients. The issue was efficacy, as study 007 results could not be supported by study 005 study results. In this review, the completed study 006 results did not reveal clinical or laboratory adverse effects of significance. The results have suggested that when the product is used for several cycles for extended periods of time, expected adverse events (increased cough, productive cough, hemoptysis, etc) tend to increase in frequency. For the original NDA submission, patients who had received multiple treatment cycles had increased levels of resistance among strains of *Pseudomonas aeruginosa* or other CF-associated bacteria. The completed study results indicated that the MIC of isolates generally returned to baseline MIC values. It is unclear what the result would be if the treatment continued beyond 18 months (i.e. 9 courses of treatment).

Based on the safety material provided for completed study 006, AI is safe for use by CF patients if approved. No additional information emerged in this review that changes our previous view of the product in terms of its safety at the end of the initial NDA review.

## Safety in On-going Clinical Studies

According to the Sponsor, the following clinical studies of AI are ongoing or have been initiated: GS-US-205-0110, GS-US-205-0117, EA-US-205-0111, EA-US-205-0122, GS-US-207-0103, and GS-US-219-0102. In addition, Gilead has provided AI to patients with cystic fibrosis (CF) and moderate to severe lung disease through a compassionate use program.

**Reviewer's Redesignation of protocol/study titles**
For the purpose of this review, the reviewer has abbreviated the Sponsor's protocol titles by redesignating them with just the last 4 figures of each protocol's title as shown in the new study table (NST) 1.

**Redesignation of protocol/study titles**

| **NST-1** | | | |
|---|---|---|---|
| № | Sponsor's Protocol | Reviewer's new designation | Comments |
| 1 | GS-US-205-0110 | 0110 | |
| 2 | GS-US-205-0117 | 0117 | |
| 3 | EA-US-205-0111 | 0111 | |
| 4 | EA-US-205-0122 | 0122 | No patients enrolled |
| 5 | GS-US-207-0103 | 0103 | |
| 6 | GS-US-219-0102 | 0102 | |
| | | | |

***MO Comments:***
*Although the Sponsor's goal is to enroll 150 patients for study 0122 (the Canadian Expanded Access Program), no patient had been enrolled at the time this 18 months safety update (of the on-going new studies) was submitted by the Sponsor. Therefore, no further discussion of the study will be done for the rest of the review.*

The on-going studies (as described by the Sponsor) are summarized in table NST-2. The study sites (countries), study design, number of patients enrolled and the number targeted to be enrolled as reported by the Sponsor are shown in the table.

| **NST-2** | **New On-Going Studies** | | | | |
|---|---|---|---|---|---|
| **Study #** | **Study Site [Length of study]** | **Phase** | **Study Design** | **Description** | **N** |
| 0110 (IND 64,402) | US, Europe [26 weeks] | 3 | OL, R, MC | Efficacy and safety of AI vs TOBI (intermittent) in patients ≥ 6 years of age with CF (x3 cycles separated by off-cycles) FB an open-label, single-arm extension | *79 (Goal =240) |
| 0117 | Canada, Australia, US, [56 days] | 3 | DB, PC, MC, R, | Efficacy and safety of AI vs placebo for one cycle (28 days) in CF patients ≥ 6 years of age with mild lung disease (FEV1 > 75% predicted) and lung *PA* | *124 (Goal = 140) |
| 0111 | U.S. Only | 3 | - | Expanded Access Program AI TID for US CF patients who have limited treatment options and are at risk for disease progression | 394 |
| 0122 | Canada only | | | Expanded access program AI TID for Canadian CF patients who have limited treatment options and are at risk for disease progression | *0* (Goal =150) |
| 0103 (IND 101,769) | US | 2 | DB, PC, MC, R, Preceded by a 28-day AI TID run-in period | Efficacy and safety of two different doses (80/20 mg and 160/40 mg) of Fosfomycin/Tobramycin for Inhalation (FTI) BID vs placebo BID for one cycle (28 days) in patients ≥ 18 years of age with CF lung disease and *PA* and $FEV_1 \geq 25\%$ and $\leq 75\%$. | 9 (Goal =120) |
| 0102 | ? | 2 | OL, R, MC | Validate the quality of life questionnaire-bronchiectasis and to evaluate perception of symptom improvement following one course of AI in subjects with bronchiectasis and Gram-negative bacteria in the airways." | 7 |
| Compassionate Use | Us, Europe, Canada, Australia | - | - | Investigator requests have been made for compassionate use of AI for patients with end stage CF. AI is being supplied to investigators for compassionate use on a case-by-case basis. | 57 |
| DB = Double blind; PC = Placebo controlled; OL = Open label; R = Randomized; TOBI = Tobramycin solution for Inhalation; FB = Followed by… *PA = Pseudomonas aeruginosa;* → = Enrollment currently up to (in July); * = Safety population in the data sent; *0* = No patient enrolled so far | | | | | |

## Study US 0110

**Deaths**
No deaths were reported for study 0110.

**Discontinuations Due to Adverse Events**
Two patients have been discontinued from this study due to AEs as of the time the data were sent to the FDA for review. One patient (6210602) was discontinued for pulmonary exacerbation; the other (7262201) was for a skin lesion. No additional information was provided.

**SAEs**
The Sponsor reports that a total of 19 SAEs have been recorded in study 0110 since enrollment began. Of these, 11 (27.5%) patients treated with AI TID reported 13 SAEs versus 4 (10.3%) patients who received TOBI who reported six SAEs. Out of the nine patients in whom pulmonary exacerbations were reported, 4 (10%) received AI TID while 5 (12.8%) received TOBI. For the other SAEs, i.e., pulmonary exacerbation, acute pancreatitis, haemoptysis, suicide attempt, lower respiratory tract infection, constipation, nephrolithiasis, inadequate control of diabetes mellitus, and postoperative fever, the Sponsor did not provide information as to who received what product.

Pulmonary excerbation was reported as the most common SAE. No SAE was considered related to study drug.

**AEs**
Table NST-3 displays the common adverse events reported in at least 5% of study patients in this particular study. Per the Sponsor, cough has been the most commonly reported AE to date, occuring in 6 (15.0%) AI-treated patients compared to 15 (38.5%) TOBI-treated patients. The the incidence of productive cough has been similar in both arms of the trial so far. The rest of the AEs are as shown in NST-3.

***MO Comments:***
*The overall SAE rate in AI-treated patients (27.5%) has been higher than in TOBI-treated patients (10.3 %). It is unclear if any meaning can be made of this in this small study. Does the regimen difference, for example, or the product difference (Tobramycin versus Aztreonam) account for the difference? Preliminary conclusions may be, perhaps, premature and speculative.*

## Study 0117

**Deaths**
No deaths were reported in this study.

**Discontinuations Due to Adverse Events**
Five patients were discontinued from this study due to AEs. One patient (0372300) was discontinued for decreased $FEV_1$; another (1603705) for a combination of cough, fatigue, decreased appetite and weight; another for pulmonary exacerbation; another (1864310) for a combination of throat irritation, chest discomfort, wheezing, and dyspnoea. For two patients (0562502 and 1323104), no reason was provided for their discontinuation.

**SAEs**
Per the Sponsor, the nine SAEs reported were considered attributable to underlying CF disease. The Sponsor did not report how many patients reported these SAEs. The events included pyrexia, bronchopneumonia, *Pseudomonas* bronchitis, pulmonary exacerbation and distal ileal obstruction syndrome.

**AEs**
In presenting patients who reported AEs, the Sponsor combined all patients together, whether they received AI or placebo. No subgroup comparisons were provided. Such comparisons likely can not be made because of blinding.The most commonly reported AEs were cough 35 (28.2%), nasal congestion 18 (14.5%), headache 14 (11.3%) and productive cough 13 (10.5%), as shown in table NST-3.

***MO Comments:***
*The Sponsor likely combined data for the AI-treated and placebo-treated patients because of study blinding. The sponsor should not be aware of who received test product versus placebo.*

## Study 0111

**Deaths**
There have been 11/394 (0.03%) deaths so far in this expanded access program. In one of the patients (03204), SAEs (rather than the death) were considered related to study drug. The cause of death was reported to be due to "end-stage cystic fibrosis lung disease".

**Discontinuations Due to Adverse Events**
Per the Sponsor, 13/394 (0.03%) patients were discontinued or their study medication discontinued due to AEs. Reasons for dicontinuation included, but were not limited to, pulmonary exacerbation, pneumothorax, respiratory failure, haemoptysis, lung transplant, and cardio-respiratory arrest.

**SAEs**
Per the Sponsor, of the SAEs that have been reported, the most frequent was pulmonary exacerbation, leading to hospitalization. Other SAEs included haemoptysis and end-stage CF lung disease. Three SAEs of haemoptysis, pulmonary exacerbation, and end-stage CF occurred in two patients and were considered by the investigator to be related to study drug.

**Study 0122**

This study is a Canadian Expanded Access Program that will serve to further expand the safety database for AI TID in Canadian CF patients who have limited treatment options and are at risk for disease progression. As no patient had been enrolled when this report was submitted for review, there are no safety data yet from this planned study.

**Study 0103**

**Deaths and Discontinuations Due to Adverse Events**
No death or discontinuation recorded thus far.

**SAEs**
No SAEs has been reported so far.

As of 31 March 2009, the Sponsor reported, 17 AEs had been recorded in three patients. Seven of those AE occurred during the AI run-in period and 10 AEs occurred during the FTI/placebo period. Each of two cases reported increased wheezing, sinus congestion, and sore throat. It is unknown who received placebo or study drug, probably due to blinding.

**Study 0102**

**SAEs**
No SAEs and no deaths have been reported as of the end of the reporting period.

**AEs**
Two AEs have been recorded to date. The two reported AEs were individual occurrences of syncope vasovagal and dyspnoea. Neither AE was considered related to study drug.

**Compassionate Use**

**Death**
A total of three deaths have been reported since the beginning of the compassionate use program, per the Sponsor.

**SAEs**
Nine SAEs for four patients have been reported during this reporting period.

| **NST-3** | **Adverse Events Reported in The On-going Studies** | | |
|---|---|---|---|
| | **Study** | | |
| | **0110** | | **0117** |
| | **AI** | **TOBI** | AI + PL |
| | **N = 40** | **N = 39** | **N = 124** |
| **Adverse Events** | n (%) | n (%) | n (%) |
| Cough | 6 (15) | 15 (38.5) | 35 (28.2) |
| Productive cough | 4 (10) | 5 (12.8) | 13 (10.5) |
| Haemoptysis | 5 (12.5) | 4 (10.3) | - |
| Pharyngolaryngeal pain | 2 (5) | 1 (2.6) | 10 (8.1) |
| Pyrexia | 5 (12.5) | 2 (5.1) | - |
| Chest discomfort | 1 (2.5) | 2 (5.1) | 7 (5.6) |
| Headache | 5 (12.5) | 3 (7.7) | 14 (11.3) |
| Nasopharyngitis | 2 (5) | 4 (10.3) | - |
| Pulmonary exacerbation | 1 (2.5) | 3 (7.7) | - |
| Myalgia | 2 (5) | 0 | - |
| Nasal congestion | - | - | 18 (14.5) |
| Rhinorrhoea | - | - | 12 (9.7) |
| Fatigue | - | - | 10 (8.1) |
| Exacerbation | 1 (2.5) | 3 (7.7) | - |
| Forced Expiratory Volume ↓ | 2 (5) | 0 | - |
| PL = Placebo; AI = Aztreonam for Inhalation. | | | |

***MO Comments:***

*It appears that the AEs reported so far in the on-going studies are similar to those generally reported in CF disease or CF patients receiving inhalational products.*

*In approaching the review of these new/on-going safety results, this reviewer was curious about whether any unsual AE types were associated with use of Fosfomycin with Tobramycin for Inhalation. But only nine patients have received the products so far in the data submitted. No conclusions can be drawn from the experience of nine patients. Therefore whatever safety results are available so far from that study may be seen in that context. Besides, the safety of AI is the primary product of interest as part of its efficacy (and safety) re-analyses.*

*The 11/394 (0.03%) deaths and 13/394 (0.03%) patient discontinuations in study 0111 relate to the number (394) of patients treated so far and, more importantly, the severity of disease of patients who often are evaluated in the expanded access programs. A sizeable number of them have end stage renal disease and some are awaiting lung transplantation.*

*Overall, therefore, the adverse events reported in the new/on-going studies derived from the data submitted by the Sponsor are probably acceptable in the management of CF patients barring emergence of more significant AEs with more extended use (e.g. years).*

## Overall conclusion

The efficacy and safety data of AI were provided by the Sponsor for the first cycle of this NDA review. The review of the safety data of the now completed study 006, an open-label study designed to provide potentially instructive safety information associated with extended AI use, has been completed. The study provided safety data of AI use for nine cycles (18 months). The initial safety results for the new and on-going studies of AI were also provided and reviewed.
The conclusions drawn following completion of study 006 review were enumerated on pages 25 through 27. Those reported from the new/ongoing studies so far do not show unexpected safety results. The AEs reported were not generally different from the AE types seen in other studies submitted for the initial NDA review.

Therefore, on a risk/ benefit assessment, the AI safety data available so far have not shown the AE profile that would constitute a barrier to product approval.

Whether AI is efficacious for the treatment of CF patients has been demonstrated in study 007 data. The adequacy of study 005 results to support study 007 data has been questioned by this reviwer. The process of determining the qualification of study 005 data to support study 007 results is primarily a scientific one, conducted rigorously. That process can also be tempered with other factors, e.g., 1.) the nature of the disease targeted for treatment, 2.) whether the disease is an unmet medical need, 3.) whether any treatment product, an alternative therapy or an adjunctive therapy currently exists for the the treatment of the disease of interest, and how well they can treat such disease.
In the case of CF, only one inhalational product (TOBI) has been approved for its treatment thus far. There is some evidence that it has been helpful for the management and improvement of a patient's lung disease and their general wellbeing. The the ultimate test of a treatment product is its ability to prevent death and prolong life. For AI, there may be some room for approval of the product based on a.) the adequacy of study 007, b.) some positive secondary findings (e.g., $FEV_1$ and other positive results) in study 005, c.) to serve as an alternative inhalational product to TOBI for the treatment of cystic fibrosis.

My resevations about the product approval, however, include the less than adequate quality of the overall study 005 data; the TID (rather BID) regimen being sought for approval as BID regimen is more convenient for use. There was some indication that BID regimen is at least as good as TID regimen, if not better. In addition, whether or when reduced susceptibility of *Pseudomonas aeruginosa* isolates to aztreonam will emerge with extended use (perhaps, months or years) is matter only time can tell, if the product is approved.

All things considered, I would be willing to consider the product for approval if the Sponsor is willing to address the concerns raised above. I would be doing so mainly to make an alternative inhalational product available for CF patients, until perhaps a more convenient regimen version of AI, or a different (perhaps, superior) product is available. I therefore recommend AI for approval. In doing so, I also hope that the sponsor is willing to commit to address the reservations expressed above as phase 4 responsibilities.

APPEARS THIS WAY ON ORIGINAL

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-50814 | ORIG-1 | GILEAD SCIENCES INC | CAYSTON(AZTREONAM FOR INHALATION SOL) |

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/s/

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MENFO A IMOISILI
02/09/2010
Safety Review of AZLI Resubmission

JOHN J ALEXANDER
02/09/2010

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** 09-15-08

**FROM:** Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

**SUBJECT**: Deputy Division Director's Summary Review Memo for NDA 50-814, lyophilized aztreonam lysine 75 mg for inhalation (Tradename CAYSTON®)

## 1.0 Background

Aztreonam is a synthetic bactericidal monobactam agent. Its mechanism of action is via inhibition of cell wall biosynthesis, resulting in cell lysis and death through irreversible inhibition of penicillin-binding proteins (PBPs). Aztreonam binds with high affinity to PBP3 of aerobic Gram-negative bacteria but has poor affinity against PBP3 of Gram-positive and anaerobic bacteria. The applicant, Gilead Sciences Inc., has submitted NDA 50-814 in support of 75 mg lyophilized aztreonam lysine for inhalation (AZLI), administered using the PARI eFlow electronic nebulizer. This application is submitted under Section 505(b)(2) of the FD&C Act, and relies on the Agency's previous findings of safety and effectiveness for the reference listed drug product, aztreonam (AZACTAM®, NDA 50-580, approved December 31, 1986). However, the application does contain new clinical studies to support the requested indication of improvement of respiratory symptoms and pulmonary function in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* (PA).

This memo will summarize elements of all reviews by discipline. For detailed discussions, please refer to the respective CMC, sterility assurance, product quality microbiology, pharmacology/toxicology, microbiology, clinical pharmacology, clinical, and biometrics reviews, and related consults.

## 2.0 Summary of Chemistry, Manufacturing, and Controls

This application is recommended for approval by the CMC reviewer, Mark R. Seggel, PhD. However, the deficiencies cited by the sterility assurance reviewer

are noted. AZLI is a sterile, lyophilized powder containing 75 mg of aztreonam. Each vial of AZLI contains a solid mixture of 75 mg of aztreonam and L-lysine, which is added (b) (4). Note that Azactam contains arginine instead of lysine, which is not well tolerated in the lung. The manufacturing process is straightforward and the finished product quality is tested for assay, content uniformity, solution pH, moisture content, impurities, sterility and endotoxin. Known degradants include (b) (4) and two (b) (4). The container closure system consists of a 2-mL USP Type I amber glass vial with a (b) (4) rubber stopper and an (b) (4) cap. The diluent consists of 1-mL sterile sodium chloride 0.17% w/v packaged in low density polyethylene (b) (4) ampules. The drug product is supplied in a carton containing a 28-day supply of vials of lyophilized aztreonam for inhalation and an equal number of ampules of the saline diluent, plus four extras in case of spillage. For long-term storage, AZLI solution should be refrigerated (2-8°C). However, once dispensed to patients, the product may be stored at 25°C for up to 28 days. A 24-month expiration dating period has been established for aztreonam vials.

At the time of submission of the NDA, one of the drug product manufacturing sites, (b) (4), had been placed under OAI status; at this time, the issues related to the OAI have been resolved. After discussions with FDA, Gilead decided to add a second drug product manufacturing site, Gilead-San Dimas. All drug substance and drug product manufacturing and test facilities were found to have acceptable cGMP statues based on inspection or profiles and an overall acceptable recommendation was make by the Office of Compliance on July 2, 2008.

## 3.0 Summary of Product Quality Microbiology

The sterility assurance reviewer, Vinayak Pawar, PhD, has identified several deficiencies to be resolved at the two drug manufacturing sites and one diluent manufacturing site, as follows:

- For drug product manufactured at Gilead-San Dimas, information is incomplete and therefore needed on drug product solution (b) (4) sterilization/depyrogenation of containers, closures, equipment and components; holding periods and media fill procedures and specifications.
- For drug product manufactured at (b) (4), a data summary from the endotoxin test validation report and updated endotoxin test results from the ongoing stability time point studies for AZLI is needed.
- For the diluent manufactured at (b) (4)., information is incomplete and therefore needed on drug product solution (b) (4) sterilization/depyrogenation of containers, closures,

equipment, and components; holding periods and media fill procedures and specifications.

The absence of the aforementioned information in the application does not provide assurance regarding potential microbial contamination of the product, and therefore the application cannot be approved until this information is provided.

## 4.0 Summary of Pharmacology/Toxicology

Based on the review of the nonclinical pharmacology and toxicology information by Dr. Amy Ellis, this application is recommended for approval. Key findings of her review include: 1) the clinical formulation of AZLI was well tolerated by dogs and rats when dosed for up to 3 months, 2) inhaled doses of aerosolized aztreonam of up to 120 mg/kg/d in a 2-year rat carcinogenicity study were not associated with increased mortality or malignancies, 3) systemic exposure to aztreonam following inhalational administration is extremely unlikely to be as high as the levels that were achieved in animal studies using IV or SC administration, 4) genetic toxicology was negative in a variety of *in vitro* and *in vivo* assays, as reported in the Azactam label, 5) impaired fertility was not observed in rats at subcutaneous doses of up to 2400 mg/kg/d, 5) aztreonam was not a sensitizer in guinea pigs following intraperitoneal induction and intratracheal challenge with the drug.

## 5.0 Summary of Clinical Pharmacology

In support of the NDA, Gilead submitted six clinical studies: two single ascending dose Phase 1 studies to assess safety, tolerability, and PK (study CP-AI-001 in healthy subjects and study CP-AI-002 in patients with CF); one double-blind, placebo controlled phase 2 study in CF patients (study CP-AI-003); and three Phase 3 studies (studies CP-AI-005, CP-AI-007, and CP-AI-006). Study 003 compared AZLI 75 mg bid and 225 mg bid to placebo for 14 days in 105 adult and adolescent (>12 y.o.) CF patients with *P. aeruginosa*. The primary endpoint for this study was % change in $FEV_1$ from Day 0 to Day 14. Studies 005 and 007 were double-blind, randomized, placebo-controlled studies comparing AZLI to placebo for 28 days. The design of these two studies differed somewhat such that 005 evaluated AZLI 75 mg tid vs. AZLI 75 mg bid vs. placebo bid vs. placebo tid after all subjects had received 28 days of open-label inhaled tobramycin. The endpoint for this study was time to need for inhaled or IV antibiotics. Study 007 compared AZLI 75 mg tid to placebo tid and the primary endpoint was change from Day 0 to Day 28 in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a Patient Reported Outcome (PRO) tool. Study 006 was an open-label, follow-on study for subjects in 005 and 007, designed primarily to evaluate the safety of multiple 28-day courses of AZLI. Subjects who had received placebo in 005 or 007 were switched to either 75 mg bid or tid of AZLI, according to whether they had received bid or tid placebo in 005 or 007.

Results of these studies will be discussed further in the section on clinical efficacy. With respect to the applicant's selection of 75 mg tid dose for marketing, the evidence to support this dose appears to be marginal. In study 003, neither of the two study drug arms was statistically superior to the placebo arm, although for the secondary endpoint of change in *P. aeruginosa* colony forming units (CFUs) in the lung, a dose-dependent effect was demonstrated such that 225 mg bid resulted in greater reduction in lung CFUs (-2.1 $\log_{10}$) compared to 75 mg bid (-1.5 $\log_{10}$). However, the clinical significance of this reduction in CFUs is uncertain. The bid arms in study 005 outperformed the tid arms for the primary efficacy analysis of time to need of IV or inhaled antibiotics.

Other key points from the clinical pharmacology review of Sarah Robertson, PharmD, include:

- In study 002, sputum concentrations of aztreonam following 150 mg AZLI were approximately double those of 75 mg, with no further increase observed at a dose of 225 mg.
- Following administration of AZLI to adult CF patients, mean plasma Tmax is achieved < 1h post-initiation of dose. The mean plasma Cmax following a 75 mg dose of AZLI is 419 ng/mL vs. a Cmax of 90 µg/mL following a therapeutic 1 g dose of IV aztreonam.
- Absorption of aztreonam following inhalation is low, with approximately 10% of the administered dose excreted unchanged in the urine, compared to 60-65% if the dose following IV aztreonam.
- Sputum levels of aztreonam are highly variable in CF patients, and concentrations in adolescent CF patients are consistently lower than in adults at all dose levels.
- In the Phase 2 and 3 studies, sputum samples were collected from patients only at 10 minutes post-dose. Thus, T>MIC cannot be determined for any of the patients enrolled in the efficacy studies and cannot be assessed with respect to efficacy outcomes.
- Serial sputum samples collected in study 002 can be used to compare sputum exposure with the $MIC_{90}$ values for *P. aeruginosa* isolated in the Phase 3 clinical trials. These observations suggest that a 75 mg tid dose of AZLI achieves a T>MIC of approximately 12% of the dosing interval in the lungs of adult and adolescent CF patients, however sputum exposure is highly variable.

The application is found to be acceptable from the standpoint of the clinical pharmacology reviewer, Sarah Robertson, PharmD. However, she notes that the proposed dose of 75 mg tid may not be the most efficacious dose for the requested indication based on data from the Phase 2 and 3 studies. She recommends should another Phase 3 trial be conducted, that a dose of 150 mg bid be evaluated.

## 6.0 Summary of Clinical Microbiology

The clinical microbiology reviewer, Dr. Peter Coderre, is unable to support approval because neither he nor the applicant could demonstrate any correlations of microbiologic outcomes to clinical outcomes. He stated that he believes the clinical endpoints should be the deciding factors in the determination of the clinical efficacy of AZLI. Dr. Coderre's conclusions are as follows:

- Patients in the study drug arms of the Phase 2 and three Phase 3 studies had lower or comparable *P. aeruginosa* (PA) loads in sputum, showed no increases in other pathogens associated with CF and had pathogens with similar $MIC_{90}$ at baseline and end of treatment.
- Changes in the numbers of PA were not associated with changes in $FEV_1$ or aztreonam concentrations in study 003 and 005, and were slightly negatively associated in study 007.
- Changes in numbers of PA in sputum were not associated with changes in aztreonam concentrations in study 003.
- Changes in aztreonam MIC for the PA isolate with the highest MIC from each patient were slightly positively associated with changes in $FEV_1$ in study 003 but slightly negatively associated in study 007.
- Changes in numbers of PA in sputum were not associated with changes in aztreonam MIC for the PA isolate with the highest MIC in studies 005 and 007.
- Changes in numbers of PA in sputum were not associated with changes in CFQ-R respiratory domain score in study 007.

Dr. Coderre notes that a similar lack of correlation of microbiology outcomes with clinical outcomes was seen with inhaled tobramycin (TOBI®) and is noted in that product's package insert.

## 7.0 Summary of Clinical Efficacy

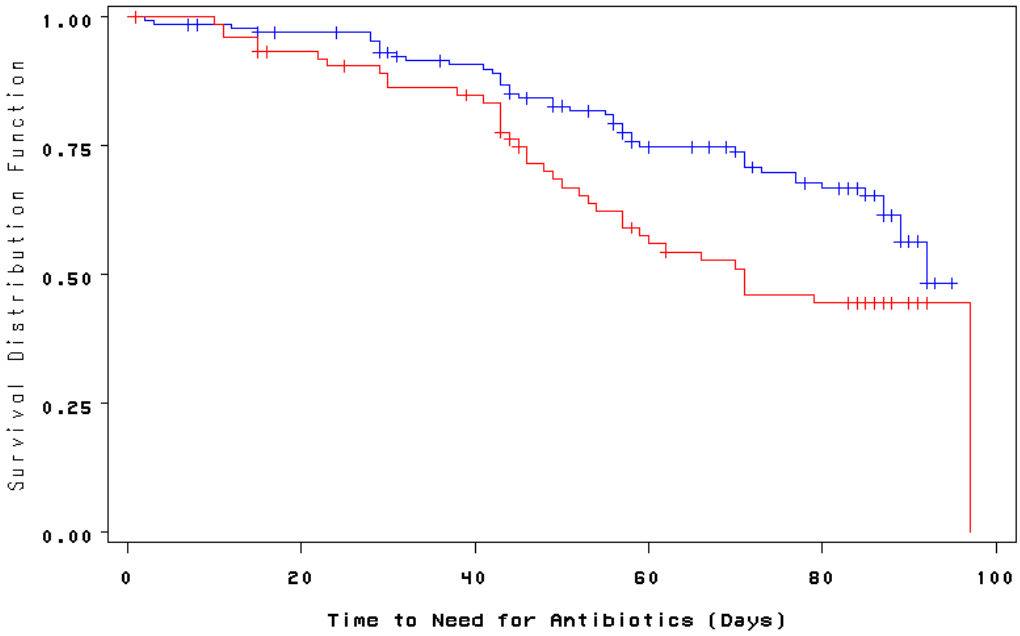
As noted previously, in support of this application Gilead submitted three Phase 3 studies (005, 007, and 006), and one phase 2 study (003). Studies 005 and 007 were the subject of Special Protocol Assessments. Numerous discussions and correspondence with the applicant stressed that study 005 was necessary to support the findings of study 007; in essence, that two adequate and well-controlled studies should be submitted to demonstrate the efficacy of AZLI for the requested indication. Although studies 005 and 007 differed somewhat in design and had different primary endpoints, both studies incorporated the primary endpoint of the other study as an important secondary endpoint. For additional details regarding the efficacy of AZLI, please see the clinical efficacy review of Dr. Menfo Imoisili, and the biometrics review of Dr. Christopher Kadoorie.

Both studies 005 and 007 were Phase 3, randomized, double-blind studies designed to evaluate the safety and efficacy of a 28-day course of 75 mg AZLI

vs. placebo in CF patients aged 6 years and older with PA and baseline $FEV_1$% predicted between 25% and 75%. Study 005 enrolled 211 subjects who were randomized 2:2:1:1 to bid and tid regimens of AZLI and placebo following 28 days of open-label inhaled tobramycin, whereas 007 enrolled 164 subjects and assessed only the 75 mg tid regimen compared to placebo. The primary endpoint for 005 was time to need for inhaled or IV antibiotics and for 007 was change from baseline in CFQ-R respiratory domain. Use of the CFQ-R was evaluated by the Study Endpoints and Label Development team and will be discussed further later in this memo. The applicant determined that a change of 5 points represented the minimum change that can reliably be detected by an individual patient on the respiratory domain scale, as determined by data from study 005.

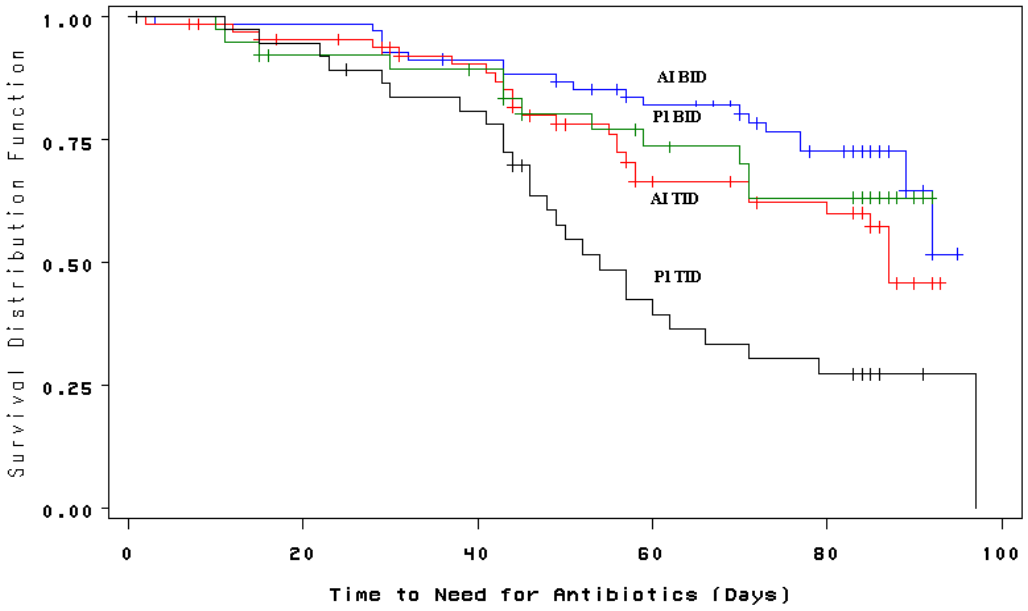
For study 005, the applicant's primary analysis considered the pooled AZLI regimens compared to a pooled placebo group, i.e. using subjects who received placebo bid and tid. The results of their analysis revealed that patients in the pooled AZLI arm had a statistically significant 21 day difference in time to need of antibiotics (p=0.007) compared to the pooled placebo arm, as shown in Figure 1 below, from Dr. Kadoorie's review.

Figure 1. Applicant's primary analysis of time to need for IV or inhaled antibiotics for the ITT population in study 005.




This approach proved problematic when our analysis of the data revealed that the two placebo groups had disparate results and therefore were inappropriate for pooling. Figure 2 below, also from Dr. Kadoorie's review, demonstrates a significant regimen effect such that ITT patients on a bid regimen achieved a greater time to need for inhaled or IV antibiotics due to pre-defined symptoms than patients on a tid regimen, regardless of whether an AZLI or placebo regimen was received. In fact, subjects in the placebo bid arm fared better than subjects in the AZLI tid arm.

Figure 2. Time to need for inhaled or intravenous antibiotics for the ITT population.




The reason for this finding is not apparent to our review team, although some concern regarding randomization of subjects prior to receipt of open-label tobramycin inhaled solution might have introduced variability in the groups. The applicant was unable to provide an adequate explanation for this finding. The analyses of the secondary endpoints were also problematic because they assessed treatment effects vs. pooled placebo as well and the AZLI bid effects were generally more favorable than the AZLI tid effects. Also, the applicant failed to control against inflation of the overall type I error rate. Because of the discrepancy between the treatment effects for the two placebo groups, the true placebo effect is unknown, and therefore comparisons between placebo and the study drug arms are uninformative. Therefore, study 005 is not adequate to provide evidence of efficacy of AZLI 75 mg bid or tid for the requested indication.

Study 007 evaluated 80 subjects who received 75 mg AZLI tid for 28 days compared to 84 subjects who received placebo. For the primary efficacy analysis of change in the CFQ-R respiratory domain at Day 28 from Day 0 for the ITT and PP populations, subjects in the AZLI arm achieved significantly higher CFQ-R respiratory scores at Day 28 compared with the placebo patients, as shown in Table 1.

Table 1. Change in CFQ-R respiratory scores from Day 0 to Day 28 for the ITT and PP population in study 007.

| | **ITT** | **PP** |
|---|---|---|
| Treatment difference AZLI-placebo | 9.71 | 6.33 |
| 95% CI (p-value) | 4.31, 15.11 (p=0.0005) | 1.22, 11.43 (p=0.0154) |

For selected secondary endpoints, the following p-values were observed: median time to need for IV/inhaled antibiotics (p=0.0949), $FEV_1$% predicted actual change from Day 0 to Day 28 (p=0.0001), mean change in weight Day 0 to Day 28 (p=0.0039), mean change in BMI Day 0 to Day 28 (p=0.0054).

When considering the efficacy results for study 007, there are a few important design issues to bear in mind. The first is that an interim analysis involving sample size re-estimation was conducted by an unblinded independent third party based on variability of CFQ-R results. Although the applicant maintains they remained blinded, the change in sample size creates a concern of potential operational bias. It also raises questions about the consistency of the findings, since the results prior to the interim analysis suggested that the sample size be increased and the results after the interim analysis led to a trial that appears to be overpowered. As noted in the statistical review, there are differences in the results by age and geographic location of the study site. Less of an effect was observed in North America compared to Investigational sites outside North America. In addition, issues with the use of the CFQ-R instrument to assess treatment effect have been identified by the SEALD team, specifically regarding the 2-week recall period which is of particular concern because children as young as 6 y.o. were enrolled and their ability to recall how they felt 2 weeks ago is questionable and the differences observed in the study were greater in patients under the age of 18 than it was in patients over 18 years of age. Another concern was the burden of the 50-item questionnaire, because of the potential for missing data. To quote from the SEALD consult by Elektra Papadopoulos, "The adequacy of the CFQ-R for this application should not be used as a firm precedent that the CFQ-R represents a standard for efficacy measurements in CF. For that reason, SEALD recommends (b) (4)

In summary, although study 007 achieved its primary endpoint and this was supported by findings for several secondary endpoints, the use of this trial alone to support approval is not warranted, due to the limitations of the CFQ-R and the use of an unblinded interim analysis as described above. The Agency has routinely required at least two adequate and well controlled studies to support the approval of an application. While there are some particular applications that may warrant approval based on a single trial, factors such as endpoints which do not

measure irreversible morbidity or mortality, study alternations based on interim analyses, and conflicting results from other studies suggest more information is needed to support this application.

The applicant has not provided data that replicate or support the results of 007, and there is information to suggest that the appropriate dose is not known. The phase 2 study 003 did not evaluate a 75 mg tid regimen, nor did it achieve its primary endpoint and therefore is also not supportive. As recommended by the clinical and biometrics reviewers, the applicant should conduct an additional phase 3 study to address this deficiency, which will be outlined in the complete response letter.

**8.0 Summary of Safety**

Dr. Menfo Imoisili's medical officer review provides an extensive discussion of the safety of AZLI and concludes that adequate safety data have been presented by the applicant to support the safe use of AZLI in patients with CF and PA. For complete information, please refer to his review. Adverse events known to be associated with Azactam use and described in the label include pseudomembranous colitis, toxic epidermal necrolysis, hypersensitivity, and thrombophlebitis, among others.

There were 537 AZLI treated subjects and patients in the NDA database of which 519 were CF patients. The size of the safety database is considered to be adequate, give the limited number of CF patients worldwide (60,000) and in the U.S. (32,000) and the information known from the agency’s findings of safety and efficacy from NDA 50-580. Among all study subjects, one death occurred due to underlying disease and recurrent hemoptysis. SAEs were reported at generally low rates and cough and productive cough were the most common SAEs. Drug-related or study procedure-related AEs leading to study discontinuation occurred more commonly in the placebo arms. The most frequently reported treatment emergent adverse events (TEAE, $\geq$ 5%) in studies 005 and 007 were cough, productive cough, nasal congestion, and dyspnea. Most TEAE rates were generally comparable across the bid and tid study arms. No significant safety signal was noted for any laboratory parameters, including hematologic parameters, transaminases, and serum glucose. No cases that met Hy's law for hepatotoxicity were noted.

**9.0 Summary of Other Regulatory Issues**

The Division of Scientific Investigations conducted audits of 2 study sites in each of studies 005 and 007. These 4 sites were selected for inspection because they enrolled the largest number of subjects. Based on the audits, the studies appear to have been conducted according to the investigational plan and the data are reliable.

DMEP has conducted a review of the label and made recommendations to improve the container label, carton and package insert labeling prior to approval. These recommendations include revising the established name in accordance with current USP salt nomenclature, revising the net quantity statement, embossing only one side of the ampule and eliminating abbreviations in the package insert labeling. The proposed proprietary name Cayston was found to be acceptable, however the proposed name will need to be resubmitted for evaluation, once the application is otherwise complete.

A 510(k) application has been submitted for the eFlow Platform Nebulizer, which is a modified and enhanced version of the FDA-cleared eFlow Electronic Nebulizer. Unlike the predicate device, the subject device is designed to incorporate a series of nebulizer configurations that will allow the eFlow to be customized for the patient and the liquid medication. For this reason, the Platform is to be used only in conjunction with those liquid medications specifically approved for use with a specific model or configuration of the device; in this case, for use with AZLI. At this time, the 510(k) review memo by Dr. Sugato De is serving as the CDRH consult and the file is on hold, pending approval of the AZLI NDA.

**10.0 Recommendation**

I concur with the recommendation of the clinical and biometrics reviewers that the application cannot be approved at this time due to a lack of substantial evidence of efficacy because the inconsistent results of the two placebo arms render study 005 uninterpretable. Study 007 is not adequate as a single study and does not provide compelling evidence of an effect on mortality or irreversible morbidity. Lastly, the phase 2 study 003 did not evaluate a dose of 75 mg tid, which is the applicant's proposed to-be-marketed dose and regimen, nor did it demonstrate a statistically significant treatment effect of AZLI on the primary endpoint of change in $FEV_1$. Therefore, an additional Phase 3 study should be conducted that confirms and supports the findings of study 007 before this application can be approved. In addition, the deficiencies noted by the product quality reviewer will need to be resolved.

Katherine A. Laessig, M.D.

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/s/
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Kathrine Laessig
9/16/2008 10:36:40 AM
MEDICAL OFFICER

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 50814 |
| Submission Code | 000 |
| Letter Date | November 16, 2007 |
| Stamp Date | November 16, 2007 |
| PDUFA Goal Date | September 16, 2008 |
| Reviewer Name | M. Austin Imoisili, MD, MPH |
| Review Completion Date | July 16, 2008 |
| Established Name | Aztreonam |
| (Proposed) Trade Name | Cayston |
| Therapeutic Class | Monobactam Antibacterial |
| Applicant | Gilead Pharmaceuticals |
| Priority Designation | S |
| Formulation | Inhalational |
| Dosing Regimen | 75 mg TID |
| Indication | Lung Disease in Cystic Fibrosis |
| Intended Population | Cystic Fibrosis Patients |

## Table of Contents

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The Sponsor submitted NDA # 50814 as a 505 (b)(2) application to evaluate Aztreonam Lysine for Inhalation (AI) for the for the improvement in the respiratory signs and symptoms and lung functions in Cystic Fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* infection.
For this application, the Sponsor subitted two Phase 3 pivotal, randomized, double-blind, placebo-controlled, multicenter studies. Study 007 was evaluated to establish the efficacy of AI in 80 CF patients who received 75 mg AI TID for 28 days and compared to 84 CF patients who received inhaled volume matched placebo administered TID also for 28 days. All 164 patients constituted the Intent-To-Treat (ITT) population. They served as the primary population for the study. The patients were assessed with a CF Questionnaire-revised (CFQ-R) patient reported outcome (PRO) tool. With this tool, improvement, or otherwise, in clinical symptoms was assessed following completion of treatment on Day 28. This was the primary endpoint. The study met its primary endpoint. A follow up visit at Day 42 was also measured. This, too, was successful. By these results, the study established the efficacy of AI.
Study 005 was conducted such that its results, if successsful, would serve to support study 007 results. Like study 007, the treatment was for 28 days. There were two regimens (BID and TID) evaluated in the study. Each regimen had an AI arm and a corresponding placebo arm (i.e. 75 mg AI BID versus Placebo BID; and 75 mg AI TID and placebo TID). The primary endpoint was time to need for an anti-pseudomonal antibiotic. Initiation of AI treament was preceded by 28 days of TOBI, intended to achieve a fairly comparable lung status at baseline.
After evaluating results of study 005, the Medical Officer (MO) has considered the results inadequate to support study 007 data. Consequently, based on this inadequate evidence, the reviewing MO recommends an action of approvable for NDA # 50814.
The MO recommends that the Sponsor conducts another Phase 3 study to corroborate study 007. Upon completion of such a study, the Sponsor is to re-submit the data from the study to the Agency for review. Future approval of AI will be contingent upon providing adequate evidence of efficacacy of AI to support the data of study 007 already reviewed and accepted by the Agency.

## 1.2 Risk Benefit Assessment

Not applicable

## 1.3 Recommendations for Postmarketing Risk Management Activities

Not applicable

## 1.4 Recommendations for other Post Marketing Study Commitments

Not applicable

# 2 Introduction and Regulatory Background

## 2.1 Product Information

The primary reason for this NDA is to evaluate aztreonam as an inhalational product intended for the improvement of respiratory signs and symptoms and lung function in Cystic Fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* (*PA)* infection. An additional goal is the hope that, if approved, the product could serve as an alternative inhalational treatment to Tobramycin Solution for Inhalation (TOBI) for use in CF patients, particularly amidst the concerns about potential emergence of aminoglycoside-resistant CF *PA* isolates.
The most significant bacterial pathogen associated with CF pulmonary disease is *PA*[1].

Aztreonam is a monocyclic β-lactam (monobactam) antibiotic and the first monobactam agent of clinical significance. It is active solely against gram-negative aerobes and stands alone among β-lactam agents in this respect. Parenteral aztreonam contains a buffer, arginine (780 mg/ gm of aztreonam). The product (aztreonam) is reported to be active *in vitro* against > 80% of *PA* strains.[2] It has also been reported that at least 12% of *PA* strains are resistant to aztreonam[3]. Aztreonam has been demonstrated to have *in vitro* activity against aminoglycoside-resistant CF pathogens.[4] Aztreonam (as Azactam®) was approved for intravenous (IV) administration in the US in 1986.

Aztreonam with arginine buffer has been administered as an injectable antibiotic product (intramuscularly and intravenously) since its approval. Aerosolized arginine has been tested as a mucolytic in CF patients and was shown to cause airway inflammation. A lysine salt was then substituted for arginine which, according to the Sponsor, eliminated the inflammatory component of the IV formulation. The Sponsor also reported that the pH and osmolality of aztreonam with lysine solution have been adjusted within parameters known to be generally safe and tolerable in the airway.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The only approved inhalational agent for the targeted indication is TOBI (see section 2.1 above).

## 2.3 Availability of Proposed Active Ingredient in the United States

The product under review, aztreonam for inhalation (AI), is the first aztreonam product formulated as an inhalational agent. Therefore, it is currently not available in the U.S. as an approved inhalational agent.
As indicated under subsection 2.1, Aztreonam (as Azactam®) was approved for IV administration in the U.S. in 1986.

## 2.4 Important Safety Issues with Consideration to Related Drugs

As this is the first aztreonam inhalational agent, no pre-existing documented safety information about this inhalational formulation of aztreonam existed prior to this NDA. Related drugs include its IV formulation and the larger β-lactam class.

The aztreonam label lists the following signs and symptoms as adverse events associated with the IV formulation of aztreonam:

**Pseudomembranous colitis -** has been reported rarely with aztreonam and may range in severity from mild to life-threatening. Patients who develop diarrhea during or following administration of aztreonam should be evaluated for this diagnosis.

**Toxic epidermal necrolysis** - has been reported rarely with the use of aztreonam in patients undergoing bone marrow transplantation. Other risk factors, such as graft-versus-host disease, sepsis, radiation therapy, and other concomitantly administered drugs, are thought to have contributed to the development of this reaction.

***Less frequent Adverse Events***

**Hypersensitivity -** anaphylaxis; skin rash, redness, or itching

**Thrombophlebitis -** discomfort, inflammation, or swelling at the injection site

***Rare Adverse Events***

**Central Nervous System:** seizures, confusion, diplopia, numbness of tongue, vertigo, tinnitus, paresthesia, insomnia, headache

**Respiratory:** dyspnea or wheezing (sometimes in association with hypersensitivity); nasal congestion

**Cardiovascular:** hypotension, electrocardiogram (ECG) changes (usually transient)

**Gastrointestinal:** stomach cramps, nausea, vomiting, diarrhea, hepatitis

**Hematologic:** neutropenia, thrombocytopenia, anemia, leukocytosis, thrombocytosis, pancytopenia
**Skin or Mucosal membrane:** urticaria, petechiae or purpura, mouth ulcers

**Musculoskeletal:** muscular aches

**Infections:** vaginal candidiasis or vaginitis
**Others:** Fever, chest pain, flushing, halitosis, diaphoresis, breast tenderness, dysgeusia

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor provided the following tables (Tables G1a and G1b) to summarize the pre-submission regulatory activities related to this application.

**Table G1a: Sponsor's Tabular Summary of Presubmission Regulatory Activities**

| Submission Date | Serial # | Submission Description | Protocol/ Statistical Information |
|---|---|---|---|
| 13 February 2004 | 016 | Initial information on investigational plan for Phase 3 | -- |
| 06 April 2004 | 020 | Briefing packet for 4/29/04 telecon | Short synopses of studies CP-AI-004 and CP-AI-005 |
| 27 April 2004 | 022 | Response to FDA questions on briefing packet | -- |
| 29 April 2004 Teleconference with Division | | | |
| 28 May 2004 | 026 | Briefing packet for 7/1/04 telecon | Short synopses of studies CP-AI-004 and CP-AI-005 |
| 01 July 2004 Teleconference with Division | | | |
| 24 August 2004 Teleconference with Division | | | |
| 09 September 2004 | 039 | Briefing packet for 9/13/04 telecon | Short synopses of studies CP-AI-004, CP-AI-005, and CP-AI-006 |
| 13 September 2004 Teleconference with Division | | | |
| 26 October 2004 | 041 | Briefing packet for 11/23/04 EOP2 meeting | Short synopses of studies CP-AI-004, CP-AI-005, and CP-AI-006 |
| 23 November 2004 End-of-Phase 2 (EOP2) Meeting with Division | | | |
| 17 November 2004 | 047 | SPA for study CP-AI-005 | Draft CP-AI-005 Protocol |
| 18 February 2005 | 052 | Response to FDA clinical and statistical comments on CP AI 005 | CP-AI-005 Protocol, Am1 CP-AI-007 Protocol |
| 25 August 2005 | 066 | Briefing packet for 9/13/05 telecon | Synopsis of study CP-AI-004 |
| 13 September 2005 Teleconference with Division | | | |
| 22 September 2005 | 069 | Request for meeting | Informed about planned sample-size re-estimation |
| 28 October 2005 | 072 | Briefing document for 11/29/05 meeting | Statistical plan summary for Phase 3 trials (CP-AI-005 and CP-AI-007) |
| 02 November 2005 | 073 | Protocol submission | Amended CP-AI-007 protocol, amendment 1 (version 3) a |

**Table G1b: Sponsor's Tabulation of Presubmission Regulatory Activities (Continued).**

| Submission Date | Serial # | Description of Submission | Protocol/ Statistical Information |
|---|---|---|---|
| 29 November 2005 Meeting with Division | | | Information on CP-AI-007 |
| 16 December 2005 | 075 | Draft minutes for EOP2 meeting | Sample size and power estimate and the draft sample size re-estimation and analysis plan |
| 09 January 2006 | 078 | Gilead response to FDA comments on sample size re-estimation | Revised sample size re-estimation and analysis plan for CP-AI-007 |
| 12 May 2006 | 088 | Response to FDA questions (received 5/4/06) | -- |
| 06 June 2006 | 090 | Protocol submission | Amended CP-AI-007 protocol, version 4b |
| 09 June 2006 | 092 | Briefing document for 7/11/06 meeting | Draft SAP for CP-AI-007 |
| 11 July 2006 Meeting with Division | | | |
| 11 August 2006 | 099 | Response to FDA questions (received 7/7/06) | - |
| 05 September 2006 | 102 | Protocol submission | Amended CP-AI-007 protocol, "new" version 4 |
| 29 November 2006 | 108 | Notification of change in SAP for CP-AI-005 | Provided a description of changes to SAP but not actual SAP for CP-AI-005 |
| 12 January 2007 | 110 | Briefing document for the 2/14/07 Pre-NDA meeting | SAP for CP-AI-005 and CP-AI-007 |
| 14 February 2007 → Pre-NDA Meeting | | | |

***MO comments:*** *The above tables (G1a and G1b) chronicle the presubmission interactions between the Division of Anti-Infective and Ophthalmology Products and the Sponsor. The application was submitted as a rolling review. The clinical portion of the review was submitted on November 16, 2007.*

## 2.6 Other Relevant Background Information

Not applicable (N/A)

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The Division of Scientific Investigations (DSI) conducted audits of 2 study sites in each of the pivotal studies CP-AI-005 and CP-AI-007. For each study, the sites were selected for inspection by the Division of Scientific Investigaion (DSI) because they enrolled the largest number of patients. They were chosen to establish absence of possible site-specific or investigator-specific irregularities that could have significant impact on overall study results. The results of such investigation were still pending at the time this review was being written. In addition, a randomly generated patient list was used 1) to ascertain the quality of data transcription from the Case Report Forms (CRFs) to the datasets, and 2) to ensure that the investigator's conduct of the trial and assessment of the patients were acceptable to the reviewer.
According to the Sponsor, the protocol, its amendments and other accompanying materials were provided to each investigator, reviewed by each institution's Institutional Review Board (IRB)/Ethics Committee (EC) to ensure that they were in compliance with US FDA regulations as well as other regulatory bodies in other countries where the studies were conducted. Documented approval from the IRB/EC was obtained before starting the trials.

## 3.2 Compliance with Good Clinical Practices

DSI inspected the largest two sites of enrollment for each of the pivotal studies CP-AI-005 and CP-AI-007. Their findings were to include evidence of consistency with good clinical practice. According to the Sponsor, the investigators were instructed to ensure that each trial was conducted in compliance with the protocol (and its amendments) and in accordance with "… the Declaration of Helsinki, the ICH guideline for Good Clinical Practices (GCP), all applicable US FDA Regulations…" as well as "… Australian TGA regulations, New Zealand Medsafe regulations, and Canadian HPFB regulations, and all other applicable local laws and regulations, as evidenced by their signatures on the protocol and the protocol amendments."

## 3.3 Financial Disclosures

The Sponsor submitted FDA form 3454 certification of financial interest for each investigator involved in the conduct of studies CP-AI-003, CP-AI-005, CP-AI-006 and CP-AI-007. Investigators were required to disclose any proprietary interest in the product used in the conduct of the studies or significant equity in the company as defined in 21 CFR 54.2(b). The Sponsor affirmed on the form that no investigator had such interest to disclose. In addition, a debarment certification, clearing the Sponsor of the use of any debarred investigator in the conduct of any their studies, was also submitted for this application.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Please refer to chemistry review by Dr. Mark Seggel.

## 4.2 Clinical Microbiology

Please refer to microbiology review by Drs Peter Coderre and Fred Marsik.

## 4.3 Preclinical Pharmacology/Toxicology

Please refer to pharmacology/toxicology review by Dr. Amy Ellis.

## 4.4 Clinical Pharmacology

### *4.4.1 Mechanism of Action*

Like other β-lactam antimicrobial agents, aztreonam interferes with the biosynthesis of the bacterial cell walls by binding to penicillin-binding proteins.

### *4.4.2 Pharmacodynamics*

Please refer to clinical pharmacology review by Dr. Sarah Robertson.

### *4.4.3 Pharmacokinetics*

Like any other CF inhalational product, the two major questions with this product were 1.) whether the systemic absorption was significant enough to engender systemic adverse effects attributable to intravenous aztreonam, and 2.) whether the product concentrations in the sputum and lung fluid were such as would allow optimum killing of *PA* and other relevant/applicable pathogens (according to age, chronicity and severity of the CF disease).
The Sponsor conducted pharmacokinetic (PK) studies of AI in CF patients in their Phase 1 studies. The following results were reported:

**Sputum**

**Adults:** The median aztreonam sputum levels in adults 10 minutes after receiving 75 mg, 150 mg, and 225 mg of AI were 383, 879, and 985 μg per gm of sputum (or, μg/gm), respectively; 4 hours later, the levels were 16, 36, and 52 μg/gm respectively.

**Adolescents:** The median sputum levels 10 minutes after receiving 75 mg, 150 mg, and 225 mg doses of AI were 324, 387, and 260 µg per/gm; 4 hours later, the levels were 2, 7, and 8 µg/gm respectively.

***MO comments:*** *The median sputum levels of aztreonam obtained were about ten times the $MIC_{90}$ (32 µg/mL) for Pseudomonas aeruginosa with all three dose levels at 10 minutes post dosing. The level remained above the $MIC_{90}$ for at least 4 hours in the adults CF patients at the 150 and 225 mg doses but not at 75 mg. The level at 4 hours was the more important measurement because, being a time-dependent antibiotic, the level of aztronam remaining above $MIC_{90,}$ at 4 hours post administration (assuming no resistance), is the desirable goal as it provides assurance of bacterial killing. However, in the adolescent patients, that level only remained above the $MIC_{50}$ (2 µg/mL) at 4 hours and in all three doses measured.*

**Serum**
**Adults:** The aztreonam plasma concentrations measured in the adult cohort following the 75 mg AI dose resulted in a mean maximum concentration (Cmax) of 426 ng/mL at 0.97 hour ($T_{max}$), a half-life ($t_{1/2}$) of 2.1 hours.

**Adolescents:** Per the Sponsor**, "**Plasma concentrations of aztreonam were studied only in adults…" in their study 002 (CSR, page 52). No explanation was provided them (the Sponsor). It is possible they felt serum concentrations of aztreonam in adults and adolescents might be comparable.

***MO comments:*** *A goal of the use of inhalational antibiotics is to provide minimal systemic absorption following pulmonary inhalation as opposed to systemic administration. For the studies submitted for this review, **t**he Sponsor provided the mean serum concentration of AI (426 ng/mL) at ~one hour ($C_{max}$) following inhalation of 75mg of the product. However, they did not provide the serum concentration (at $C_{max}$) following systemic (I.V. or I.M) administration of 75mg aztreonam to allow geometric mean comparison of both. The Azactam® label provides serum aztreonam concentrations after systemic administration of higher doses. (e.g., 500 mg, 1 gm, etc.). The serum concentrations are given in micrograms/mL (not nanograms/mL as provided after inhalation). This suggests that the difference between aztreonam levels following systemic administration versus administration by inhalation may be something in the order of 1000 times (if inhaled product is at all detectable in the serum).*

# 5 Sources of Clinical Data

## 5.1 Tables of Clinical Studies

Table G2 enumerates the studies conducted by the Sponsor. The studies comprise two Phase 3 pivotal double-blind, placebo-controlled studies; one Phase 3 open-label follow-on safety study; one Phase 2 proof-of-concept study; and two Phase 1 safety, tolerability and pharmacokinetic (PK) studies, one of which was conducted in healthy adults.

## Table of Clinical Studies

**Table G2** **Tabular Listing of All Clinical Studies**

| Protocol /Phase | Objective | Study Design | Regimen [By Inhalation] | N | Duration (Days) |
|---|---|---|---|---|---|
| CP-AI-007<br><br>Phase 3 | Assessment of Safety and Efficacy of AI | Double-blinded, Multicenter, Randomized, Placebo-Controlled Trial with Aztreonam for Inhalation (AI) in Cystic Fibrosis Patients With Lung Disease Due to *P. aeruginosa* Infection. | 75 mg TID | Total = 164<br>[AI→80<br>PCB→84] | AI = 28<br>Follow up =14 |
| § CP-AI-006<br><br>Phase 3 | Safety<br>$1^0$ = AEs: airway reactivity, vital signs, and lab.<br>$2^0$ = Disease related Endpoints: $FEV_1$ and CFQ-R lung function testing. | Open-label follow-on study (patients from CP-AI-005 and -007). Patients received AI corresponding to the regimen (BID or TID) received in the study whence they came. | 75 mg TID<br><br>OR<br><br>75 mg BID | Total = 207<br>[AI:<br>BID →82<br>TID→125] | AI = 28 (one course). And history of up to 9 courses with 28 days off AI between 2 consecutive courses. |
| CP-AI-005<br><br>Phase 3 | Assessment of Safety and Efficacy of AI<br>$1^0$ = Time to need for inhaled or I.V. antibiotics. $2^0$ = Disease related | Double-blinded, Multicenter, Randomized, Placebo-Controlled following 28 days of Tobramycin Solution for Inhalation (TSI/ TOBI) use. | 75 mg TID<br><br>OR<br><br>75 mg BID | Total = 211<br>AI:<br>BID →69<br>TID→66<br>BID (PCB) →38<br>TID (PCB) →38 | 28-day run-in of TOBI followed by 28 days of AI and 56 days of follow-up. |
| CP-AI-003<br><br>Phase 2 | Assessment of Safety and Efficacy of AI<br>$1^0$ = % change in $FEV_1$ (Day 0 through Day 14) | Double-blinded, Multicenter, Randomized, Placebo-Controlled. | 75 mg BID<br><br>OR<br><br>225 mg BID | Total = 105<br>AI:<br>75 mg BID →37<br>225 mg BID→37<br>PCB BID →31 | 14 days of AI; then,<br><br>14 days follow-up<br><br>(CF patients) |
| CP-AI-002<br><br>Phase 1b | Assessment of Safety, Tolerability; Pharmacokinetic study | Double-blinded, Multicenter, Randomized, Placebo-Controlled. | 75mg→150 mg<br>↓<br>225 mg/day<br>& daily escalation over 3 consecutive days. | Total = 35<br>AI→23<br>PCB→12 | 3 days of AI;<br>Then,<br>3 days of follow-up (CF patients) |
| Phase 1a | Assessment of Safety, Tolerability; Pharmacokinetic study | Double-blinded, Multicenter, Randomized, Placebo-Controlled. | 1st cohort→95 mg<br>2nd cohort→190 mg<br>3rd cohort→285 mg<br>3 cohorts escalation | Total = 24<br>95 mg→ 6<br>190 mg→ 6<br>285 mg→ 6<br>PCB→ 6 | Single dose per subject (healthy adults); then<br>3 days of follow-up |

**§: Study on-going – only interim data reported, PCB = Placebo;** AE= Adverse event; Lab = Laboratory; I.V. = intravenous;

**Study Centers**

Table G3 lists the the number of study centers, the geographic locations of the centers and the time period in which the studies were conducted. Only study CP-AI-001 was conducted entirely outside of the U.S. Forty of the 53 centers in which study CP-AI-007 was conducted were in the U.S.; the rest were in Australia (7 centers), Canada (5) and New Zealand (1). All other studies were done in the U.S. One hundred and twenty-five patients were enrolled in the U.S and in Canada for study CP-AI-007 alone. In the same study, 39 patients were enrolled in Australia and New Zealand (18 patients received AI and 21 patients, placebo). A consult was sent to the Division of Scientific Investigation (DSI) to evaluate two centers that enrolled the largest number of patients in each of the two pivotal studies (CP-AI-005 and CP-AI-007) submitted for efficacy evaluation of AI. The goal was to ascertain potential investigator-related or site-specific inadequacies or irregularities that could have impact on overall study results.

**Table G3 - Study Centers: Number, Location and Periods/Dates of Study**

| Protocol (Phase) | Number of Centers | Geographic Locations | Study Period/Dates |
|---|---|---|---|
| CP-AI-007 | 53 | USA, Canada, Australia, and New Zealand | First enrollment: June 10, 2005<br>Last follow-up: April 3, 2007<br>Database lock: May 15, 2007 |
| CP-AI-006 | 54 | U.S.A. only | First enrollment: August 17, 2005<br>Study still ongoing; submitted data collected on or before March 1 2007 |
| CP-AI-005 | 56 | U.S.A. only | First enrollment: February 24, 2005<br>Last follow-up: September 7, 2006<br>Last database relocked: February 28, 2007 |
| CP-AI-003 | 20 | U.S.A. | First Randomization: November 25, 2003<br>Last follow-up: August 4, 2004<br>Database lock: September 16, 2004 |
| CP-AI-002 | 8 | U.S.A. | Study period: May through October, 2003 |
| CP-AI-001 | 1 | U.K. | Study period: November 13 through December 7, 2002. |
| | | | |

Following their site inspection, the Division of Scientific Investigation (DSI), in response to our consult, sent the following preliminary report on June 18, 2008:

*In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable. Final classifications of Clinical Investigator inspections of Dr.Nakamura, Dr. Billings, and Dr. Trapnell are No Action Indicated (NAI). Safety and efficacy data from these clinical investigators are considered reliable. The preliminary classification of Dr. Liou is NAI, which suggests that safety and efficacy data from this site may also be considered reliable; however, final classification is pending for this site and will be determined when the final EIR and associated exhibits are received. Should the final classification for Dr. Liou be different from the current preliminary classification of NAI, the Division will be notified and an inspection summary addendum will be generated.*

## Type of submission

The Sponsor submitted this as a 505 (b)(2) application. We (Agency representatives) are relying on our previous findings of efficacy and safety of the previously approved aztronam arginine (azactam®) intravenous formulation for the review of the product. However, the primary source of the data we relied on for evaluation of the safety and efficacy of AI were generated from the study results submitted by the Sponsor.
Genotoxixity and human reproductive studies were not required for this submission as these had been conducted for the approval of azactam®.
In life-threatening infections, up to 2000 mg of azactam may be administered to adult patients intravenously every 6 to 8 hours. In less severe infections, 1000 mg is usually administered to adult patients intravenously every 8 hours.
This knowledge influenced our permission to allow the Sponsor to use 75 mg of inhalational aztreonam TID for their studies in CF patients. Although inhalational products explored so far have been associated with limited systemic absorption, in the case of AI, even 100% systemic absorption would still be much less than one dose of i.v. fomulation used on a regular basis in clinical practice. Pharmacokinetic (PK) studies conducted by the Sponsor showed limited systemic absorption. In a sense, the PK studies served as the bridging studies to the Azactam® product.

## 5.2 Review Strategy

The studies reviewed for this NDA application were enumerated in table G1. All six studies were reviewed for safety information. The two double-blind, placebo-controlled, multicenter, randomized Phase 3 pivotal studies, CP-AI-005 and CP-AI-007, were reviewed (separately) for efficacy determination of AI. Study CP-AI-005 was conducted to corroborate study CP-AI-007. The two major differences between the two studies were as follows:

**1. Differences in primary efficacy endpoint assessment methods**
In study CP-AI-005, the primary endpoint was measured by the length of time to need inhaled or i.v. anti-pseudomonal antibiotics (other than study drug) by study patients for the treatment of documented symptoms predictive of pulmonary exacerbation. Results were then compared across study arms. Whereas, in study CP-AI-007, the primary efficacy endpoint was measured by determining changes in clinical symptoms, as assessed by the the Cystic Fibrosis Questionnaire – Revised (CFQ-R), a patient reported outcome (PRO) tool. The assessments were made from Day 0 (baseline) through Day 28.

**2. Dosing regimen differences**
Patients received twice (BID) or three times (TID) daily regimens in study CP-AI-005 while study CP-AI-007 used only a TID regimen.

**3. Other differences – TOBI use in one study; length of follow up of study patients**
In study CP-AI-005, patients received a 28-day TOBI run-in period prior to receiving AI (from Day 0 to Day 28) BID or TID daily. These study patients were subsequently followed for

additional 56 days. Study CP-AI-007 patients received no TOBI prior to the receipt of AI; they were followed until day 42 following the first day of receipt of AI.

Other studies reviewed included: 1.) an open-label follow-on Phase 3 study (study CP-AI-006) which comprised patients enrolled from CP-AI-005 and CP-AI-007 after their discontinuation or withdrawal from these studies. The study served the purpose of gathering additional safety data while also allowing patients to receive the potential benefit of the product; 2.) the only Phase 2 study (CP-AI-003) where patients received 14 days of either AI or placebo; and lastly, 3.) the 2 Phase 1 studies – all for safety information.

## Order of Review

### Efficacy Review

The order of presentation of efficacy information was in accordance with the new CDER Clinical Review Template sections and subsections. Under each section and subsection, materials have been been presented in the following sequence:

1. Study CP-AI-007 (primary endpoint evaluation) was presented first as this was the study in which study patients received the to-be-marketed regimen (75 mg TID). The idea was to weigh the adequacy and strength of available evidence provided by the study to establish product (AI) efficacy during its use in study patients. The primary efficacy endpoint determination was based on information accumulated from the use of a patient reported outcome (PRO) tool, CFQ-R (descibed under section 6.1.1), for patient assessment. This instrument was used to determine the adequacy of efficacy of AI.

2. Study CP-AI-005 (primary endpoint evaluation) was presented next. This was to ascertain the strength of evidence provided by the supportive study and to determine whether it was robust enough to support or corroborate study CP-AI-007 for approval.

3. Study CP-AI-007 – secondary endpoint information (and other endpoints as relevant), was evaluated under the "Analysis of Secondary Endpoint(s)" section (i.e., section 6.1.5) to determine agreement or consistency with primary endpoint findings.

4. Study CP-AI-005 – secondary endpoint data (and other endpoints as relevant), were also evaluated like # 3 above (i.e., under section 6.1.5) to determine consistency with primary endpoint finding; it was also to determine if the data were in general agreement with study CP-AI-007 data.

The rest of efficacy review followed that pattern in accordance with the the titles and subtitles in the sections and subsections of the review template.

### Safety Review

For the safety review, safety information was also presented in accordance with the new CDER clinical review template. Study data were pooled or combined for review in the following manner:

- The 2 Phase 3 double-blind studies (CP-AI-007 and CP-AI-005) where patients received AI/placebo for 28 days were pooled and reviewed together;
- The only Phase 2 study (CP-AI-003) where patients received AI/placebo for 14 days was reviewed separately;
- The open-label Phase 3 study (CP-AI-006) was also reviewed separately;
- The 2 Phase 1 studies, were reviewed together.
- Literature materials submitted were screened for additional useful/relevant information.

**Study Name Re-designation for the Purpose of this Review**
To simplify reference to any of the studies submitted by the Sponsor, the protocol designations of individual studies were changed as shown in Table G4. The new protocol names were used for the rest of the review.

| **Table G 4** | **Study Name Re-designation for Review Purposes** |
|---|---|
| **Sponsor's Designation** | **Reviewer's New Designation** |
| Protocol CP-AI-007 | Study 007 |
| Protocol CP-AI-006 | Study 006 |
| Protocol CP-AI-005 | Study 005 |
| Protocol CP-AI-003 | Study 003 |
| Protocol CP-AI-002 | Study 002 |
| Protocol CP-AI-001 | Study 001 |

## 5.3 Discussion of Individual Studies

The goal of Gilead's development program was to evaluate a 28-day course of AI (75 mg TID) and, if approved, to eventually market it for use in patients with CF. To that end, two Phase 3 placebo-controlled efficacy trials (Study 007 and Study 005) were conducted in 375 patients altogether, primarily for efficacy (but also for safety) evaluation of AI ; moreover, an ongoing open-label follow-on study (CP-AI-006) was conducted in 274 patients, primarily for safety evaluation. At study entry, patient groups were comparable in demographic characteristics: age, gender, weight, disease severity, *PA* susceptibility to aztreonam and other characteristics that could potentially affect clinical responses. A phase 2 dose-heterogeneous, BID-regimen-specific, double blind, placebo-controlled, duration-truncated (for 14 days duration only) study was also conducted which was evaluated mainly for safety information.

The 2 Phase 3 pivotal studies (005 and 007) have been discussed under subsections 5.1 (under Tables of Clinical Studies). The results are reviewed under section 6 below.

## Study 006

Study 006 was the third Phase 3 study submitted as part of the NDA and was reviewed for safety information only. It is still an ongoing, open-label follow-on study evaluating the safety and effects on disease-related outcomes of repeated exposure (up to nine 28 day courses) to 75 mg of AI administered BID or TID. Eligible patients from the two randomized studies 007 and 005 received AI at the same regimen to which they had been previously assigned. Key outcome

measures included change in $FEV_1$, CFQ-R Respiratory Symptoms score, and sputum *PA* density. According to the Sponsor, in over six 28-day courses of therapy (alternating with 28-day off-treatment period), a trend toward improvement in each measure was observed while patients were on treatment compared to while off treatment. The Sponsor also reported that a sustained response was observed over multiple courses of therapy; moreover, that clinical improvements were more robust in the TID group than in the BID group. Lastly, they reported that patients who originated from study 007 (receiving TID regimen) seemed to have demonstrated more robust improvements in respiratory symptoms, pulmonary function, and sputum *PA* density than did patients from study 005 who received AI/placebo preceded by 28 days of TOBI. Like the other studies, increased cough and productive cough were the major AEs. There was one death in the study but relationship to study drugs could not be established. Hospitalization due to pulmonary exacerbations accounted for most SAEs.

**Study 003**
This Phase 2 blinded, multicenter, randomized, placebo-controlled trial was designed to inform the choice of AI dose, regimen(s) and duration of use to be evaluated in the Phase 3 pivotal trials. It also informed the selection of what the to-be-marketed dose and regimen should be. The Sponsor explored safety and efficacy of a 14-day treatment with AI BID compared to placebo in CF patients with pulmonary *PA* infections. Up to 138 CF patients were initially planned to be randomized into three cohorts (75 mg AI, 225 mg AI, and placebo). Patients were screened for inclusion in the 7 days preceding the start of the study. Patients self-administered the first dose and one of the Day 7 doses at the clinic, and the remaining doses were self-administered at home. Patients returned to the clinic at the end of the treatment period (Day 14) and again at Day 28 follow-up visit.
There was a loss of power in the trial as only 105 patients were evaluable in the ITT dataset - less than the planned sample size of 138. The lower enrollment was apparently not safety-related. Consequently, study results showed no statistical significance. The study led the Sponsor to pick 75 mg dose, TID regimen as the to-be-marketed dose – as they believed this would allow longer time above MIC (AI being a time-dependent antibiotic) and expected a greater bacterial killing.

**Study 002 and Study 001**
These were Phase 1 studies. Study 002 was conducted in CF patients and Study 001, in healthy adults. They were primarily for the determination of PK, tolerance and for gathering initial safety data.

# 6 Review of Efficacy

## Efficacy Summary [ES]

Study 007 was the pivotal study that provided results which were evaluated to determine the efficacy of AI in the treatment of CF patients with *PA* in their lungs. Study 005 was conducted to provide evidence to support or corroborate the results of study 007. Therefore, this review was done with two objectives in mind: 1) whether study 007 results adequately established the efficacy of AI in the treatment of CF patients with *PA* in their lungs and, 2) whether study 005 results provided adequate evidence to support the results of study 007.

# Study 007

## Design and methodology

In study 007, 164 CF patients (7 years and older) were enrolled from the US, Canada, Australia, and New Zealand. Investigators randomized 80 patients to received 75 mg of AI TID for 28 days and 84 to receive volume-matched placebo administered TID also for 28 days. All 164 patients constituted the Intent-To-Treat (ITT) population. They served as the primary population. Results gathered from the 80 patients who received AI were compared to those of the 84 who received placebo to establish the efficacy of AI according to whether the primary (and secondary) efficacy endpoints were met. Patients were assessed on Days 0, 28 and 42. On completion of the 28-day treatment, patients were followed for additional 14 days to determine if clinical improvement attained by Day 28, if any, was sustained and to what degree. Study patients were required to abstain from antibiotic use (including azithromycin) for at least 28 days before treatment. In addition, patients who used hypertonic saline were excluded. Overall, patients enrolled in this study had taken fewer than 2 TOBI courses in the 12 months preceding the initiation of study. This population was considered to be less exposed to prior inhaled antibacterial treatments for CF patients than study 005 patients.

The primary efficacy endpoint for this study was change or improvement at Day 28 (from Day 0, or baseline) in the respiratory symptoms as measured by the respiratory domain of the Cystic Fibrosis Questionaire-Revised (CFQR) for Child/Teen/Adult combined, a patient reported outcome (PRO) tool. The tool was a validated, CF-specific symptom scale that measured study patients' perception of change in their respiratory symptoms and quantified such change by the use of a standardized scoring system, the *Minimally Clinically Important Difference* (MCID). The CFQ-R respiratory domain scores ranged from 0 to 100. On this particular scale, a change of five points represented the minimum change (either improvement or decline) that was reliably detectable by the individual patient. Such a change was considered clinically meaningful improvement (if improved) or clinically significant worsening (if patient deteriorated).

# Results

**Primary Efficacy Endpoint Evaluation:** Table 007- ES1 shows the results of primary efficacy endpoint assessments, as reported by the Sponsor. At Day 28, the treatment difference in the adjusted mean between AI-treated patients (7.08) and the placebo arm patients (-2.63) was 9.71 points. This demonstrated clinical and statistical significance ($p = 0.0005$).
A greater proportion of patients in the AI group showed improvement in CFQ-R respiratory domain score (MCID of $\geq 5$ point increase) at Day 28 (56%) compared with patients in the placebo group (37%), $p = 0.0055$. This suggested a clinically significant improvement in respiratory symptoms for AI-treated patients.
To determine if this clinical treatment benefit was sustained, the the treatment difference in the adjusted means between AI-treated patients and placebo-treated patients was determined at Day 42. This demonstrated that the treatment difference seen at Day 28 had dissipated but some amount (6.33 points) persisted through Day 42. It was still statistically significant ($p = 0.0154$).

**Table 007- ES1. – Modified Sponsor's Table of Primary Efficacy Endpoints and Their Results inStudy 007**

| Primary Efficacy Endpoint Results | Result | | | |
|---|---|---|---|---|
| | 75 mg AI (N = 80) | Placebo (N = 84) | Treat. Diff. | p-value |
| **Clinical symptoms as assessed by CFQ-R respiratory domain** | | | | |
| Mean (adj) change in CFQ-R respiratory domain score at Day 14 | 7.01 | -0.98 | 7.98 | 0.0006 |
| Mean (adj) change in CFQ-R respiratory domain score at Day 28 | 7.08 | -2.63 | 9.71 | 0.0005 |
| Categorical result: % of patients who improved at Day 28 | 56.3 | 37.3 | - | 0.0055 |
| % of patients who worsened at Day 28 | 25.0 | 44.6 | - | |
| Mean (adj) change in CFQ-R respiratory domain score at Day 42 | 0.62 | -5.71 | 6.33 | 0.0154 |
| **adj = adjusted; Treat. Diff. = Treatment Difference; - = not applicable.** | | | | |

## Subgroup analyses within primary endpoints

A comparison of study patients who received AI versus placebo within specific subgroups were analyzed using the respiratory and other domain scores of the CFQ-R. The respiratory domain scores results were analyzed and the results are presented in table 007- ES2. As the table indicates, aside from the treatment effect result in the CF severity subgroup with $FEV_1 \leq 50\%$ predicted, results in all other subgroups showed statistical significance, to different degrees. The treatment difference between AI-treated patients and placebo-treated patients also appeared clinically significant relative to MCID.

**Table 007- ES2. Analyses of primary endpoint in Subgroups**

| Categorical change in CFQ-R Respiratory Domain Scores from Day 0 to Day 28 in ITT Population (Imputed Data) | | | | | |
|---|---|---|---|---|---|
| | | Adjusted Mean Change | | | |
| **Subgroup** | **Subgroup Division** | **AI Arm** | **Placebo Arm** | **Treatment Diff.** | **P-value** |
| **Disease severity** | $FEV_1 \leq$ **50% predicted** | 4.22 | -4.03 | 8.25 | = 0.0839 |
| | $FEV_1 >$ **50% predicted** | 10.14 | -0.76 | 10.9 | = 0.0018 |
| **Region** | U.S./ Canada | 5.89 | -1.47 | 7.36 | = 0.0223 |
| | Australia/New Zealand | 11.65 | -5.64 | 17.29 | = 0.0037 |
| **Age Group** | ≥ 18 | 4.82 | -1.53 | 6.35 | = 0.0495 |
| | < 18 | 12.73 | -6.19 | 18.92 | = 0.0006 |
| **Gender** | Male | 5.96 | -3.22 | 9.18 | |
| | Female | 10.76 | -0.43 | 11.19 | |
| **Highest Aztreonam *MIC*** | ≤ 8 µg/mL | 7.31 | -0.06 | 7.37 | |
| | > 8 µg/mL | 8.87 | -2.56 | 11.43 | |

Within subgroups, the magnitude of treatment effect seemed much larger in patients < 18 years of age than in adult patients. The same was true for region regarding patients from Australia and New Zealand compared to North American patients. Seasonal differences between northern hemisphere (North America) and southern hemisphere (Australia and New Zealand) accounted for the differences in results in these geographic regions. The study was being conducted at the same time that different seasons (e.g., winter versus summer) were the prevailing conditions in areas on opposite sides of (and relatively far away from) the equator.
The other binomial subgroup parameters were generally comparable.

## Secondary Efficacy Endpoints

Several secondary endpoints were explored in the study. The Sponsor-designated key secondary endpoints which included 1) pulmonary function ($FEV_1$) changes, 2) requirement for additional antipseudomonas antibiotics by study patients, 3) change in $Log_{10}$ PA CFUs in the sputum, 4) hospitalizations, and 5) changes in weight and body mass index (BMI) at Day 28. Table 007-ES3 displays the bottom line results.

Pulmonary function ($FEV_1$) improved in patients treated with AI compared to the placebo arm; the treatment difference at Day 28 for percent change in $FEV_1$ was clinically significant at 10.3% and was statistically significant ($p < 0.0001$). Although treatment difference dissipated in the following two weeks, up to 5.7% was retained through Day 42. It was still statistically significant ($p = 0.0024$).
Results of forced vital capacity [FVC (L)] and forced expiratory flow rate - during the middle half of expiration [$FEF_{25-75}$ (L/sec)] were gathered as "Other Secondary Efficacy Endpoints" to further support $FEV_1$ results at Days 28 and 42. As shown in table 007- ES3, they showed consistency with $FEV_1$ results.

Regarding change in $log_{10}$ PA CFUs in sputum at Day 28, sputum density decreased (improved) to the degree that the treatment difference at Day 28 between patients treated with AI (adjusted mean = -1.384) and those who received placebo (adjusted mean = 0.069) was -1.45. It was statistically significant ($p < 0.0001$). However, at Day 42, there was no difference between treatment groups (-0.069 $log_{10}$ CFUs, $p = 0.8218$).

[Although not shown in table 007- ES3, the Sponsor also reported that there were significant differences between the AI and placebo groups at Day 28 regarding the following nonrespiratory domains of the CFQ-R: physical functioning (4.17 treatment difference [p = 0.0373]), vitality (8.33 treatment difference [p = 0.0282]), emotional functioning (6.67 treatment difference [p = 0.0030]), eating disturbances (0.00 treatment difference [p = 0.0007]), and health perceptions (11.11 treatment difference [p = 0.0002]). The MCIDs for these domains have not been established.]

The percent of patients who used IV or inhaled antipseudomonal antibiotics was slightly lower in the AI group (15%) compared to the placebo group (23%). However, this difference was not statistically significant. The percentage of patients who used oral antipseudomonal antibiotics in the AI group (11%) was lower than in the placebo group (25%), and this difference was statistically significant ($p = 0.0267$). Overall, the percentage of patients in the AI group who used antipseudomonal antibiotics of any type (oral, inhaled or IV; 18%) was lower than in the placebo group (36%), and this difference was statistically significant ($p = 0.0131$).

There was a trend towards fewer patients being hospitalized from Day 0 to 42 in the AI group than in the placebo group (4 [5.0%] vs 12 [14%], $p = 0.0640$). In addition the mean duration of hospitalization was shorter for patients in the AI group than in the placebo group (0.5 days vs 1.5 days). This too was statistically significant ($p = 0.0487$).

The predominant cause of hospitalization in both treatment groups was pulmonary exacerbation of CF disease. There were no differences between treatment groups in missed school and/or work due to CFor for change in patient's ability to produce sputum.
With respect to change in weight, as shown in table 007- ES3, the difference between the AI and placebo groups in percent change in weight at Day 28 was 1.010. It was statistically significant (p = 0.0039), with the AI group showing a greater mean gain in weight than the placebo group.. Similar results were seen for changes in BMI.

**Table 007- ES3. Secondary Efficacy Endpoint Results**

| Disease severity category | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| **Change in pulmonary function** | | | | |
| Mean (adjusted) percent change in $FEV_1$ at Day 28 | 7.9 | -2.4 | 0.3 | < 0.0001 |
| Mean (adjusted) percent change in $FEV_1$ at Day 42 | 3.1 | -2.6 | 5.7 | = 0.0024 |
| | | | | |
| **Other pulmonary function testing results supporting $FEV_1$** | | | | |
| Actual change in FVC (L) at Day 28 | 0.112 | -0.090 | 0.201 | = 0.0163 |
| Actual change in FVC (L) at Day 42 | 0.021 | -0.112 | 0.133 | = 0.1005 |
| Actual change in $FEF_{25-75}$ (L/sec) from Day 0 - 28 | 0.159 | -0.064 | 0.223 | < 0.0001 |
| Actual change in $FEF_{25-75}$ (L/sec) from Day 0 - 42 | 0.094 | -0.052 | 0.146 | = 0.0081 |
| | | | | |
| **Change in $log_{10}$ PA CFUs in sputum** | | | | |
| Mean (adj) change in sputum $log_{10}$ *PA* CFUs at Day 28 | -1.384 | 0.069 | -1.453 | < 0.0001 |
| Mean (adj) change in sputum $log_{10}$ *PA* CFUs at Day 42 | -0.078 | -0.010 | -0.069 | NS |
| | | | | |
| **Use of antispeudomonal antibiotics** | | | | |
| % of patients requiring IV or inhaled antibiotics | 15.0 | 22.6 | - | NS |
| % of patients requiring oral antibiotics | 11.3 | 25.0 | - | = 0.0267 |
| % of patients requiring antibiotics overall | 17.5 | 35.7 | - | = 0.0131 |
| | | | | |
| **Hospitalization** | | | | |
| № (%) hospitalized at least once between Day 0 and Day 42 | 4 (5.0) | 12 (14.3) | - | = 0.0640 |
| Mean number of hospitalization days (Day 0 to Day 42) | 0.5 | 1.5 | - | = 0.0487 |
| | | | | |
| **Weight** | | | | |
| % Mean percent change in weight (kg) at Day 28 | 1.076 | 0.046 | 1.010 | = 0.0039 |
| | | | | |
| **BMI** | | | | |
| Mean change in BMI ($kg/m^2$) at Day 28 | 0.213 | 0.008 | 0.202 | = 0.0054 |
| № = Number; NS = Not significant; % = percent. | | | | |

No overall correlation was observed between baseline aztreonam MIC and three key efficacy parameters (CFQ-R respiratory domain score, $FEV_1$, and *PA* sputum density). The $MIC_{90}$ was 4-fold higher for patients with a CFQ-R respiratory domain score change of ≥ 5 points. Baseline *PA* susceptibility to aztreonam did not correlate with $FEV_1$ response. Baseline $MIC_{50}$ and $MIC_{90}$ were 4-fold lower for patients with ≥ 0.75 decrease in $log_{10}$ *PA* CFUs, suggesting a correlation between baseline *PA* susceptibility to aztreonam and degree of *PA* killing.

All patients with baseline aztreonam MIC > 256 μg/mL experienced an improvement in CFQ-R respiratory domain score and 5/7 patients demonstrated either an improvement or no change in $FEV_1$ at Day 28. No correlation between baseline *PA* susceptibility to aztreonam and change in *PA* sputum density was observed for this highly aztreonam-resistant population. Therefore, it was not possible to establish a therapeutic breakpoint for AI in the study.

# Efficacy Conclusion for Study 007

After reviewing the efficacy results of study 007 the clinical reviewer has drawn the following conclusions regarding the study.

**Primary efficacy endpoints:**

1. The primary efficacy endpoint of the study, change in CFQ-R respiratory domain score at Day 28 was met. As the MCID for CFQ-R respiratory domain score was 5.0, patients treated with AI experienced clinically meaningful improvements in their respiratory symptoms, as measured by the CFQ-R.CFQ-R scores at Day 28 which were higher in AI treatment group compared to patients who received placebo. The treatment difference between the two treatment groups seen at Day 28 was 9.71. It was statistically significant ($p < 0.0001$). Results for the PP population were similar to those for the ITT population, with a treatment difference of 9.93 ($p = 0.0009$).

2. After study patients completed (inhalational) treatment, the treatment effect (adjusted mean) for AI-treated patients dropped from 7.08 at Day 28 to 0.62 at Day 42. Whereas, the adjusted mean for patients who received placebo deteriorated from -2.63 at Day 28 to -5.71 at Day 42. The mean CFQ-R respiratory domain score at Day 42 had returned to near baseline values for AI-treated patients. The difference between AI and placebo, however, remained high. This was probably due to continued deterioration of placebo-treated patients. And the treatment difference (a comparative value) between the two study groups was 6.33 ($p = 0.0154$). It was statistically significant. Thus, Day 42 results. could have been due to continued deterioration of placebo-treated patients in addition to some of the improvement seen at Day 28 in AI-treated patients being maintained for at least two weeks following discontinuation of therapy.

## Subgroups analysis (within the primary efficacy endpoints)

3. For patients in the milder disease category ($FEV_1 > 50\%$ predicted), those who received AI treatment showed clinically and statistically significant improvement from baseline compared to those who received placebo. In patients with more severe disease category ($FEV_1 \leq 50\%$ predicted), there was no statistically significant difference between treatment groups.

4. The improvement in quality of life among AI-treated patients was greater in patients in Australia and New Zealand than those in the US and Canada. The Sponsor believes difference is probably attributable to seasonal differences. Accordingly, per the Sponsor,

"the majority of the patients in both regions enrolled between August and February, corresponding to fall/early winter in the northern hemisphere and spring/early summer in the southern hemisphere. Improvements in respiratory symptoms in the patients enrolled during the fall and winter months might be attenuated due to concomitant viral infections during these months." The explanation appears reasonable.

5. The differences in improvement in respiratory status and overall quality of life following the receipt of AI compared to placebo was greater (and was stastically significant) in younger patients (< 18 years of age) than in adult patients (≥ 18 years of age).

6. There were significant differences between the AI and placebo groups for change from Day 0 to Day 28 for the following nonrespiratory domains of the CFQ-R: physical functioning, vitality, emotional functioning, eating disturbances, and health perceptions, with patients receiving AI showing more improvements.

## Secondary Efficacy Endpoints:

7. The improvement in pulmonary function, by $FEV_1$ measurement, led to an adjusted mean change in AI-treated patients of 7.886 compared to placebo arm (adjusted % mean change, -2.408) at Day 28; the treatment difference was 0.294 and was clinically significant (< 0.0001). The treatment difference attained at Day 28 dwindled following completion of therapy. However some improvement was still sustained through Day 42 and was statistically isignificant (p = 0.0024).

8. Forced Vital Capacity [FVC (L)] and forced expiratory flow rate during the middle half of the expiration [$FEF_{25-75}$ (L/sec)] were other pulmonary function tests conducted to further support $FEV_1$ results at Days 28 and 42. Although FVC (L) was not statistically significant at Day 42, both were significant at Day 28, and $FEF_{25-75}$ was significant at Day 42. Taken together, the trends showed consistency with $FEV_1$ results.

9. The mean $log_{10}$ *PA* CFU at baseline and mean $log_{10}$ *PA* CFU sputum density values were nearly equivalent in the AI and placebo groups. In the AI-treated group, $log_{10}$ *PA* CFU sputum density had decreased by more than 1.5 $log_{10}$ *PA* CFUs by Day 28. $Log_{10}$ *PA* CFU sputum density in the placebo group remained near baseline values at Day 28. Treatment difference was statistically significant (p <0.0001). At Day 42, two weeks after completion of therapy, $log_{10}$ *PA* CFU sputum density had returned to near baseline values in both the AI and placebo groups.

10. The percentage of patients who used oral antipseudomonal antibiotics in the AI group (9 [11%] patients) was lower than in the placebo group (21 [25%] patients); the difference between the treatment groups was statistically significant (p = 0.0267). Additionally, the percentage of patients in the AI group (14 [18%] patients) who used antipseudomonal antibiotics (overall) was lower than in the placebo group (30 [36%] patients); the difference between the treatment groups was also statistically significant (p = 0.0131).

11. The difference between treatment groups in the incidence of hospitalization over the 42-day trial period was not significant; however, the difference between treatment groups in the mean number of days hospitalized was statistically significant (p = 0.0487). Most hospitalizations were for pulmonary exacerbations.

12. Weight is an important predictor of mortality in CF patients. There was a significant difference between the AI and placebo groups for percent change in weight at Day 28 (1.0%, p = 0.0039), with patients in the AI group showing greater adjusted mean weight gain (1.1%) compared to those in the placebo group (0.1%).

13. There was a significant difference between the AI and placebo groups for change in BMI at Day 28. Patients in the AI group showed greater adjusted mean increase (0.213) in BMI than those in the placebo group (0.011) at that timepoint. There was a significant difference between the AI and placebo groups for change in BMI at Day 28 (0.202 kg/m2, p = 0.0054).

## Reviewer's comments on Study 007

This is the first study that has used a patient reported outcome tool to evaluate primary efficacy endpoints in study patients for the treatment and improvement of signs and symptoms of lung disease in cystic fibrosis patients. Study 007 is an adequate and well controlled study and has provided data showing that AI is efficacious for this claim. Although clinical evidence of efficacy has been provided, the data alone do not constitute adequate evidence for approval of the product for marketing. Data from another adequate and well controlled study must be provided to demonstrate reprodicibility of study 007 results. That was what study 005 was designed to provide.

# Efficacy Summary (Continued) - Study 005

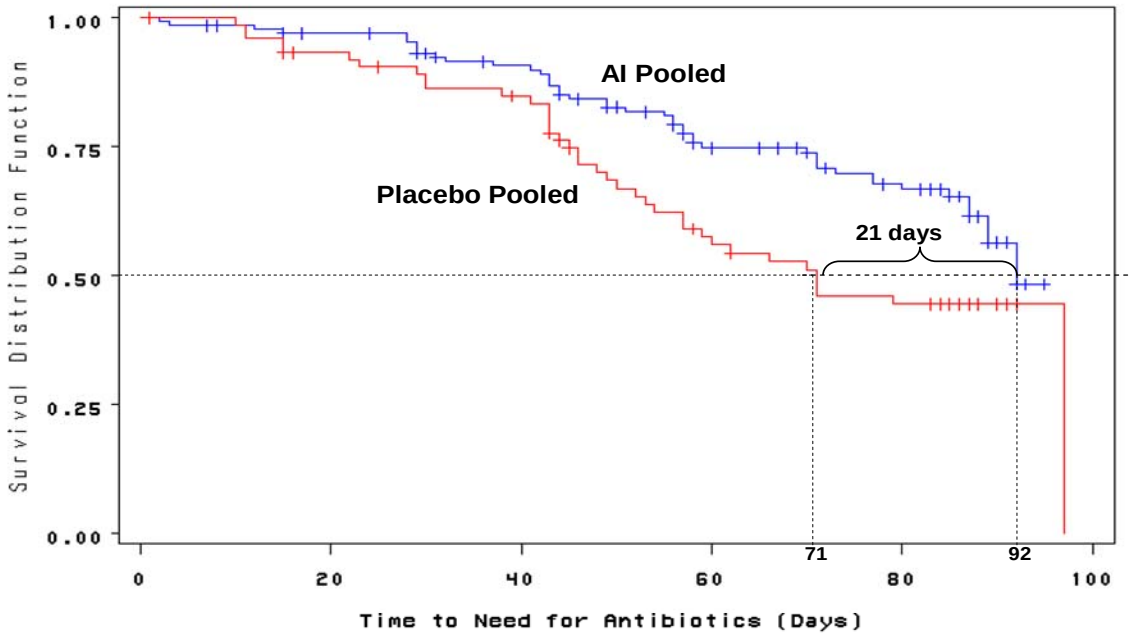
**Design and methodology**

Study 005 design was different from that of study 007. Following the screening period, patients in study 005 were randomized to four arms (AI BID, AI TID, placebo BID and placebo TID) as they would receive AI or placebo following 28 days of TOBI treatment. The completion of TOBI treatment marked the baseline for receiving AI/placebo. Altogether, 211 patients received AI or placebo in the study. Of these, 135 patients received AI; 76 received placebo. In the AI group, 69 (51%) received the BID regimen; 66 (49%), the TID regimen. Of the 76 in the placebo group, 34 (50%) each received either placebo BID or TID.

The rationale for the use of TOBI prior to receiving AI/placebo was to put all patients at the same level at baseline prior to receiving AI or placebo BID or TID. Study 007 patients received no such treatment as they were all going to receive the same dose and regimen (75 mg TID versus placebo TID). Most importantly, the primary efficacy endpoint was to determine how long it took patients receiving AI or placebo to need antipseudomonal antibiotics as a result of the development of pre-specified symptoms that are known to signal the onset of pulmonary exacerbation.

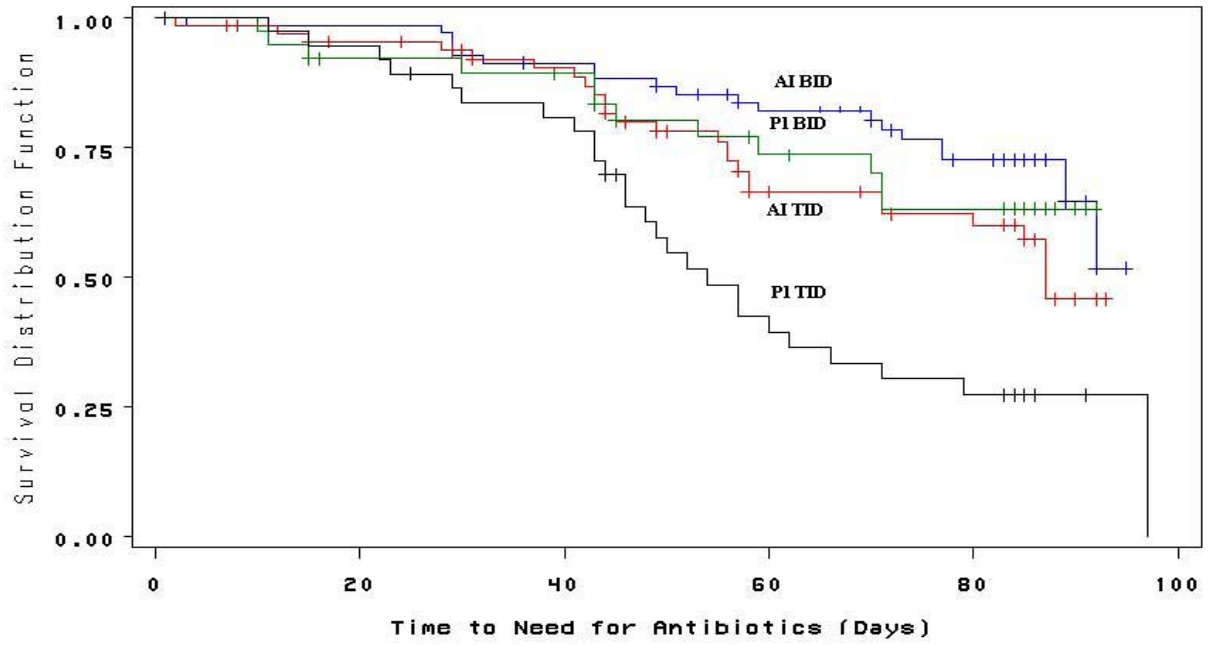
**Study 005 Results**

**Figure 005 ES1**




When the AI BID and AI TID results are pooled, and compared to the pooled placebo results (BID plus TID), we obtain the picture portrayed in figure 005 ES1 above. It would then appear that the median time to need for inhaled or IV antipseudomonal antibiotics due to pre-defined symptoms was 21 days - longer in the pooled AI group (92 days) than in the pooled placebo group (71 days) ($p = 0.0070$). The median time to antibiotic need for the AI BID group would appear significantly different from that in the pooled placebo group ($p = 0.00190$).
The study would then appear as if it has met its primary efficacy endpoint goal - until one looks at how the individual arms of the study performed relative to one another as shown in figure 005 ES2 below.

**Figure 005 ES2: Kaplan-Meier Survival Curve for the Four Subgroup Regimens KeyK**




Key for Figure 005 ES2
AI BID = Patients who received AI BID
AI TID = Patients who received AI TID
PL BID = Patients who received placebo BID
PL TID = Patients who received placebo TID

In the analysis of primary efficacy endpoint, as the Kaplan-Meier survival curve for the four study-arm regimens shows, there was a strong regimen effect (BID vs TID) which was confirmed by a post hoc analysis showing that the time to need for inhaled or IV antibiotics was different between one placebo arm (BID) and the other placebo (TID) arm.
The expectation was that placebo arms (be they BID or TID) would be very similar in performance at the end of the day which would also reflect on the Kaplan-Meier survival curve configuration.
Based on the results, the Sponsor did a post-hoc analysis using study result to highlight the strength of the regimen effect seen in the study. Table 005-ES 1 shows the Sponsor's analysis of the regimen effect.

**Table 005-ES 1 (Modified Sponsor's Table 17): Regimen Effect – A Post Hoc Analysis**

| Time to Needing Antipseudomonal Antibiotics: Regimen Effect → ITT Population | | |
|---|---|---|
| **comparison** | **Event Rate** | **p-value** |
| **Test for regimen effect** | | |
| BID vs TID** | 31/107 vs 50/104 | 0.0012 |
| Placebo BID vs placebo TID | 12/38 vs 26/38 | 0.0043 |
| AI BID vs AI TID | 19/69 vs 24/66 | 0.0835 |
| **Pooled AI vs pooled placebo stratified by regimen** | 43/135 vs 38/76 | 0.0067 |
| **Test for treatment effect within regimen** | | |
| AI BID vs Placebo BID | 19/69 vs 12/38 | 0.4269 |
| AI TID vs Placebo TID | 24/66 vs 26/38 | 0.0043 |

****Combined placebo and AI BID vs combined placebo and AI TID**

## Reviewer's comments on Study 005

A placebo-controlled study is designed so that an active product can be compared to the placebo. That presupposes that the placebo has a neutral effect on the disease of interest. That neutral effect is expected to be consistent whether the placebo is administered BID or TID. Incorporation of placebo in a study is also to limit potential biases. Therefore, results of a placebo-controlled study allow a measure of treatment effect of an active product compared to non-treatment (or placebo treatment) of the disease.

In study 005, performance of placebo BID regimen was better than AI TID. There seemed to be a strong regimen effect in the study in favor of BID regimen. Accordingly, placebo BID regimen performed better than AI TID regimen as shown in figure 005-ES2 and table 005-ES 1. Of the four regimens in the study, placebo TID was the worst performing regimen. Placebo BID seemed at variance with placeboTID. As a result it is unclear if the the true placebo effect is the placebo BID, placebo TID, pooled placebo or none of the three. It is unclear. whether the true placebo is any the three (placebo BID, placebo TID or pooled placebo) or none of the three. That is, the true placebo is unknown. Therefore any comparisons to placebo are probably erroneous.

**Study 005 patient responses seen in Kaplan-Meier Survival Curve (Fig. 005 ES2)**
In accordance with study design, study 005 patients were to receive AI/placebo BID and AI/placebo TID regimens after each patient received a 28-day course of TOBI which preceded the receipt of AI/placebo. The idea was to allow all patients to be at comparable levels at baseline before being randomized to the four AI/placebo treatment arms. Rather, the patients were randomized before receiving TOBI as opposed to just before receiving AI/placebo. The study patients, as would be expected, could have responded to different degrees of improvement following the receipt of TOBI. The situatuation lent itself to creatng patient heterogeneity in lung

status at the threshold of receiving AI/placebo. This probably affected AI/placebo treatment arms differently from this point onward as there was no opportunity to randomize at this point which could have neutralized this patient heterogeneity at baseline. This crucial error at a wrong randomization point in the study in all probability affected each study arm of study 005 and, therefore, had adverse impact on study results. Consequently, any analysis of any study arm, or comparison to any placebo arm, is potentially unreliable or even erroneous.

Based on the above issue, no credible analysis of the primary efficacy endpoint, and for that matter, secondary efficacy endpoints, can be made in study 005. Therefore, the reviewer does not agree with the primary or secondary efficacy endpoint analyses by the Sponsor.

The reveiwer would have accepted this analysis if the following criteria were met:

1. **If the true placebo effect were known or if there were consistency in placebo BID/TID arms**
   In the way study 005 was designed, the performance of the placebo arms (BID and TID) ought to be roughly similar, variability not withstanding. Placebo is placebo. Under that circumstance, pooling the placebo data would make no difference regarding such placebo serving as a comparator. Were there such consistency in placebo arms, any comparison of AI-treated group or subgroup with such a placebo comparator would be appropriate and meaningful. The placebo data from study 005 begs the question which placebo group/subgroup – BID, TID, the pooled placebo, or none of the three, represents the true placebo effect. It is unclear.

2. **If the only comparator arm was a placebo TID arm and performed in similar terms as placebo effect in study 007.**
   The Sponsor did indicate that they would explore BID and TID regimens prior to the study 005. It was uncertain and unpredictable how any of the two arms would perform individually or relative to each other. It was however expected that, being placebo, the two arms should be roughly similar regardless of any inherent, within-study variabilities. The Sponsor plans to market a TID regiment of AI (as in study 007).

## Final Comments

A need exists to provide an inhalational antipseudomonal antibiotic product to CF patients to serve as an alternative product to TOBI, the only inhalatinal antipseudomonal antibiotic approved for use so far in the treatment of chronic lung disease in CF patients. Having an alternative toTOBI is important, particularly in light of the emergence of aminoglycode-resistant *PA* isolates – a problem with a potential to get larger with continued TOBI use overtime.

The reviewer had hoped that inhalational aztreonam could be that product. However, the issue raised above disqualifies study 005 results. The results cannot serve as corroborative evidence to support the results of study 007 for approval of AI for the indication stated by the Sponsor.

## Reviewer's Recommendations

The following statements represent the revierwer's recommendions:

1. NDA #50814 is considered approvable.

2. Based on results, study 007 has provided clinical evidence to establish the efficacy of AI for use in the treatment and improvement of respiratory signs and symptoms and lung functions in CF patients with chronic *Pseudomonas aeruginosa* infection.

3. The reviewer and the review team do not accept the results of study 005 as acceptable or adequate evidence to support study 007 data. Therefore, another study is recommended to provide adequate evidence to support study 007 data and the approval of AI.

4. The study recommended should be similar in design to study 005, but to have modifications that avoid the weaknesses of study 005.

# Efficacy Analysis

## 6.1 Indication

For the improvement in the respiratory signs and symptoms and lung functions in Cystic Fibrosis patients with chronic *Pseudomonas aeruginosa* infection.

### *6.1.1 Methods*

As indicated in section 5.2, the two Phase 3 pivotal studies reviewed for efficacy determination of AI for the proposed indication were studies 007 and 005. They were double-blind, multicenter, randomized, placebo-controlled studies. In study 007, patients received three times a day (TID) regimen. This is the AI regimen proposed to be marketed. Study 005 patients received both twice daily (BID) and TID regimens.

## Study 007

After 7 to 14 days of screening, randomized patients in study 007 received either AI or placebo TID for 28 days (see figure 007-1). The primary efficacy endpoint was change in clinical symptoms (as assessed by the respiratory domain of the CFQ-R) from Day 0 (baseline) to Day 28. There was additional follow up for 14 days post-treatment.

**Study 005**

Following a 14-day screening period, all randomized patients in this study received a 28-day run-in of TOBI that led to Day 0. Patients received the the first dose of AI or placebo on Day 0 and administered BID or TID daily for 28 days (see Figure 005-1). The primary endpoint was

measured by the length of time to need an antipseudomonal antibiotic (whether inhaled or I.V.) for the treatment of symptoms predictive or indicative of pulmonary exacerbation.
The study protocol and the Agency's previous agreement with the Sponsor regarding the conduct of the study and analyses of study results were reviewed.The Sponsor's analyses of data were evaluated. The reviewer verified that the study was conducted and the data analyzed according to study protocol. The reviewer also did independent analyses of selected data for comparisons with the Sponsor's analyses. The data submitted were evaluated to determine if the primary endpoint was met regarding the efficacy of AI. Data were also evaluated for all secondary endpoints of study 005.

**Differences in Design between Study 007 and Study 005**
Although the two pivotal studies are generally similar in design, major differences between them are appreciable in Figures 007-E1 and 005-E1 as follows:

1. The two studies differed with regard to their primary endpoints: study 005 measured the median length of time to need antipseudomonal antibiotics (I.V. or inhalational) following a 28-day course of AI; the primary endpoint for study 007 involved measurement of patients' respiratory well being using a PRO tool (CFQ-R) following a 28-day course of AI.

2. Study 005 had two treatment regimens - BID and TID; study 007 had one – TID only.

3. All study 005 patients received mandatory TOBI treatment for the 28 days leading up to Day 0 (baseline).Then they received AI or placebo from Day 0 to Day 28; study 007 did not incorporate no mandatory prior TOBI treatment to the study design leading to receipt of AI/placebo treatment.

4. In study 005, patients had to have received $\geq 3$ previous courses of TOBI within the previous 12 months for eligibility. There was no such requirement in study 007 protocol. From the dataset, most study patients who had received TOBI within 12 months prior to the study had received $\leq 2$ courses. Indeed, up to $\approx 52\%$ of study patients had no documentation of receipt of TOBI within 12 months of study 007 initiation.

5. The follow-up period after completion of AI treatment in study 005 was 56 days. Altogether, the study had nine scheduled visits in the 126 days of the trial. Study 007 had only a 14-day follow-up period after the 28-day AI treatment; the study had 5 scheduled visits within the 56 days of study duration.

6. Administration of antipseudomonal antibiotics by inhalation, intravenous or oral routes (including azithromycin) as long as there had had been no change within the previous 3 months was allowed in study 005 patients; it was not allowed within the previous 28 days, particularly within 14 days prior to Visit 1 in study 007.

These two studies and all other studies submitted for this application were reviewed for safety. The other studies included 1) an open-label Phase 3 follow-on study (comprising patients who

completed participation in studies 005 and 007); 2) the only Phase 2 study (003) where patients received 14 days of either AI or placebo and 3.) the 2 Phase 1 studies.

**Figure 007-E1. Study 007: Trial Design - Scheme of Study Visits**.

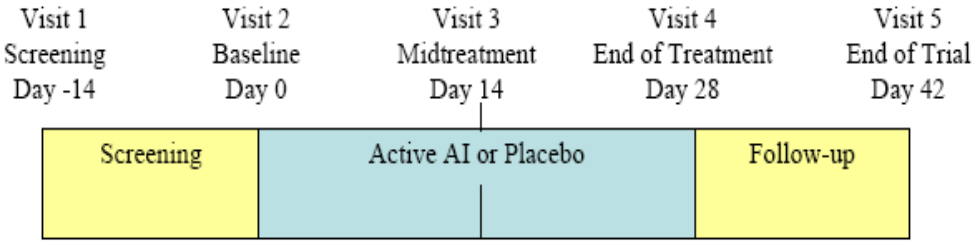
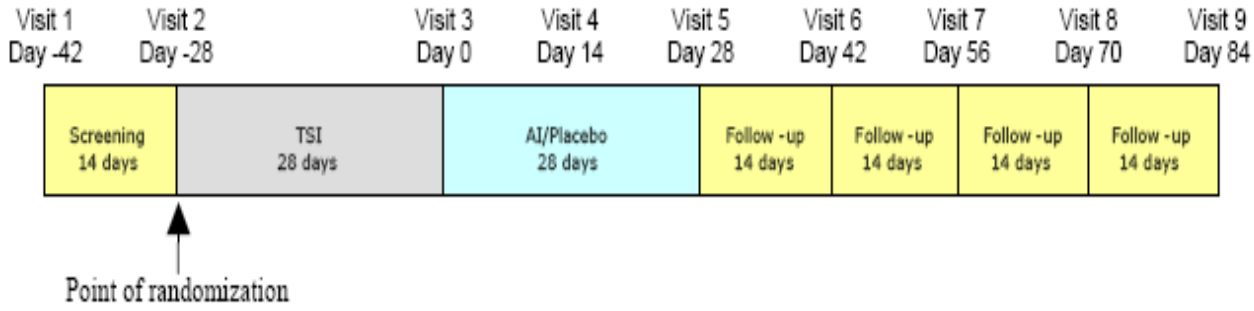



**Figure 005-E1. Study 005: Trial Design - Scheme of Study Visits**.




**Cystic Fibrosis Questionnaire-Revised (CFQ-R)**

The CFQ-R is a CF-specific quality of life measuring tool containing both generic and CF-specific domains. Four versions of the questionnaire were used by the Sponsor in studies 005 and 007. Altogether, these CFQ-Rs encompass domains for evaluating physical functioning, role limitations/school performance, vitality, emotional functioning, social functioning, body image, eating disturbances, treatment burden, health perceptions, weight disturbance, respiratory symptoms, and digestion. The number of domains varies with the CFQ-R version.
The four versions used in the studies under review included:

- Children ages 6 to 11 years (interviewer format; administered by the trial coordinator)
- Children ages 12 and 13 years (child format; completed by the patient)
- Adolescents and adults, ages 14 years and older (teen/adult format; completed by the patient)
- Parents/caregivers for children ages 6 to 13 years (parent format; completed by the patient's parent/caregiver). [Spanish translations of the CFQ-R were provided for parents, when necessary].

For children aged 6 to 11 years, two questionnaires were to be completed at each time point (one completed by the trial coordinator and the other completed by the parent/caregiver). For children aged 12 and 13, two questionnaires were also completed at each timepoint (one by the child; the other by the parent/caregiver). The same parent/caregiver was to complete the CFQ-R at every visit. Each questionnaire took approximately 15 minutes to complete. The Sponsor reported that patients were made aware that they were to answer the questions based on their own experience with CF, rather than general experience that was unrelated to CF. They were also reminded to answer the questions to cover the time periods outlined for each set of questions.
The questionnaires were amended for use in the trial to include trial-specific information (visit dates, patient trial identifiers, and signature pages, etc.).

The **GRCQ instrument**
Global Ratings of Change Questionnaire (GRCQ) is a health-related quality of life measuring instrument consisting of 10 questions to provide a global assessment of health outcomes for interpreting and confirming generalized findings about quality of life. It has 3 items that assess the overall effect according to whether a patient experienced any change in activity limitation, symptoms, or feelings since beginning treatment, using a 7-point scale. It has been used to establish the minimally clinically important difference (MCID) for evaluation of studies or measuring a global ratings change in health status. This instrument can also be used to focus on specific domains of health such as dyspnea, depression, etc. The GRC establishes ranges for changes in questionnaire scores that correspond to moderate and large changes in the domains of interest.
The GRCQ has been used to measure change in relevant domains over the previous two weeks as perceived by the respondent (patient or physician). This instrument measures change on a scale of -7 to 7. Positive values usually indicate improvement. Negative values indicate worsening status. No change is anchored at zero.

**Correlation of GRCQ and CFQ-R**
The Sponsor reports that the teen/adult and combined child/teen/adult versions of the CFQ-R respiratory domain were correlated well with both the GRCQ physician and patient assessments of the respiratory scale at all timepoints. The child version was correlated well with the GRCQ physician and patient assessments of the respiratory scale at Day 14, but not thereafter.

**Pulmonary function Testing**
Spirometry was performed on Days -28, Day 0, and Day 14. At such times, it was performed before treatment and 30 minutes after treatment was completed. If a patient experienced a decrease in forced expiratory volume in 1 second (FEV1) of 15% or more from pretreatment value, spirometry was repeated at 90 minutes after treatment was completed. FEV1, forced vital capacity (FVC), and forced expiratory flow from 25% to 75% of the forced vital capacity (FEF25-75) were recorded at all scheduled visits according to American Thoracic Society (ATS) guidelines. Participants performed at least three spirometry maneuvers in accordance with ATS standards. The best FEV1 and FVC were recorded, even if from different efforts. The value recorded for FEF25-75 was to be taken from the effort that produced the highest sum of FVC plus FEV1 values. The Knudson equation was used to calculate $FEV_1$ % predicted normative

values for each patient. Standard equipment and quality control procedures were used across all trial sites.
Before each pretreatment spirometry, all patients received a short-acting broncodilator (BD) within 15 minutes of spirometry performance. The BD was administered in the presence of the investigator/research nurse. Patients who normally used a BD continued their use as prescribed; however these patients were instructed to refrain from using short-acting inhaled BDs (such as albuterol) for 6 hours before each trial visit since they were to receive a dose in the clinic.

### *6.1.2 Demographics*

**Study 007**

Table 007-E1 shows the demographic characteristics of patients who participated in study 007. The Sponsor indicates that there were no significant differences between the AI and placebo groups in any demographic characteristics tested.

**Gender:** Although there were slightly more male than female patients in each study arm, the ratios were comparable across study arms.

**Race:** As expected, and as in study 005, the majority of patients were Caucasian and there was no difference in the racial composition between treatment groups.

**CF Genotypes:** The Sponsor reported that there were no statistically significant differences between treatment groups with respect to CFTR genotype ($p = 0.1076$), although a higher percentage of patients was homozygous for the ΔF508 mutation in the AI group than in the placebo group (54% vs 43%, respectively).
About 30% of the patients were heterozygous for the ΔF508 allele and another mutation. The remaining patients in each treatment group were catigorized as “unidentified”, or “other”.

**Age group:** The Sponsor reported that the mean age (± SD) of patients in the trial was 29.6 (± 14.0) years. Seventy-seven percent of the patients in the trial were 18 years or older. In the AI group there were 11 (14%) children (age category ≥ 6 years to ≤ 12 years) versus 4 (5.0%) in the placebo group. The percentage of adolescents (> 12 years to < 18 years) was similar in the two groups (13% and 14% patients for AI and placebo, respectively). The treatment comparison for age was not statistically significant ($p = 0.1386$).

**Disease severity:** The majority of patients in each treatment group fell in the milder of the two disease severity categories (i.e., those with $FEV_1$ % predicted > 50%); 64% of these patients were in the AI-treated group comparewd to 63% in the placebo-treated group. For patients in the more severe disease category ($FEV_1 \leq 50\%$ predicted), patient distribution was comparable across study arms on Day -14.

The demographic characteristics of patients in the PP population were generally similar to those for patients in the ITT population. Demographic characteristics were generally balanced between the two treatment groups.

**Table 007-E1: (Mod.Sponsors Table 5) Demographic Characteristic**

| **Table 007-E1 (Mod.Sponsor's Table 5)** | **Demographic Characteristics at Day -14: ITT Population for Study 007** | | |
|---|---|---|---|
| | **Treatment Groups** | | |
| **Variable** | **AI** | **Placebo** | Total |
| | **(N = 80)** | **(N= 84)** | **(N = 164)** |
| **Gender; n (%)** | | | |
| Male | 48 (60.0) | 45 (53.6) | 93 (56.7) |
| Female | 32 (40.0) | 39 (46.4) | 71 (43.3) |
| **Race; n (%)** | | | |
| Caucasian | 76 (95.0) | 82 (97.6) | 158 (96.3) |
| Hispanic | 4 (5.0) | 2 (2.4) | 6 (3.7) |
| **Genotype; n (%)** | | | |
| Homozygous** | 38 (54.3) | 30 (42.9) | 68 (48.6) |
| Heterozygous** | 21 (30.0) | 22 (31.4) | 43 (30.7) |
| Unidentified | 9 (12.9) | 18 (25.7) | 27 (19.3) |
| Other | 2 (2.9) | 0 | 2 (1.4) |
| **n** | 70 | 70 | 140 |
| Missing data § | 10 (12.5) | 14 (16.7) | 24 (14.6) |
| **Age group (years); n (%)** | | | |
| ≥ 6 to ≤12 | 11 (13.8) | 4 (4.8) | 15 (9.1) |
| >12 to <18 | 10 (12.5) | 12 (14.3) | 22 (13.4) |
| ≥ 18 | 59 (73.8) | 68 (81.0) | 127 (77.4) |
| | | | |
| Mean Age (yrs); (SD) | 27.4 (12.8) | 31.7 (14.8) | 29.6 (14.0) |
| | | | |
| **Disease severity; n (%)** | | | |
| FEV1 % predicted ≤ 50% | 30 (37.5) | 30 (35.7) | 60 (36.6) |
| $FEV_1$ % predicted > 50% | 50 (62.5) | 54 (64.3) | 104 (63.4) |
| ** = (ΔF508); Mod = modified | | | |

***MO Comments:*** *Among the patient subcategory with "unidentified" CF genotype, the subgroup proportion of patients who received placebo was twice as large as the subgroup proportion that received AI (AI subgroup, 12.9% versus placebo subgroup, 25.7%). The potential impact of having "unidentified" genotypic CF or/and the subcategory imbalance on the overall study result is unclear. With regard to age group, the proportion of patients in the ≥ 6 to ≤12 age bracket who received AI was more than double the proportion that received placebo (13.8% vs 4.8%). These numbers were fairly small by comparison with the much larger group of patients who were ≥ 18 years in age where the percentages of patients that received AI versus those that received placebo were 73.8% versus 81.0% respectively. These rates are more comparable.*

**Table 007-E2: (Derived: Sponsor's Table 7) Baseline Demographic Characteristics at Day 0: ITT Population^**

| Variable | Treatment Groups | | |
|---|---|---|---|
| | **AI** | **Placebo** | Total |
| | **(N = 80)** | **(N= 84)** | **(N = 164)** |
| Mean (± SD) weight (kg) | 59.91 (17.27) | 60.68 (15.18) | 60.30 (16.18) |
| Median (range) BMI ($kg/m^2$) | 21.17 (13.2, 42.3) | 21.32 (14.2, 38.7) | 21.20 (13.2, 42.3) |
| Mean (± SD) $FEV_1$ % predicted | 54.38 (13.39) | 54.83 (14.03) | 54.62 (13.68) |
| Mean (± SD) CFQ-R respiratory domain score | 60.45 (18.05) | 60.88 (18.88) | - |

- = not available; ^ = for all data, except where stated otherwise

***MO Comments:*** *As table 007-E2 indicates, the mean (± SD) for weight, BMI, $FEV_1$ % predicted as well as CFQ-R respiratory domain score for study patients are comparable across study arms on Day O, the start of AI treatment.*

**Table 007-E3: (Modified Sponsor's Table 7) Baseline Characteristics at Day 0: ITT Population[b] – Microbiology**

| Variable | Treatment Groups | | |
|---|---|---|---|
| | **AI** | **Placebo** | Total |
| | **(N = 80)** | **(N= 84)** | **(N = 164)** |
| Highest aztreonam MIC for *Pa* in sputum; n (%) | | | |
| ≤ 2 µg/mL | 23 (33.3) | 28 (36.8) | 51 (35.2) |
| 4-8 µg/mL | 15 (21.7) | 22 (28.9) | 37 (25.5) |
| 16-128 µg/mL | 24 (34.8) | 25 (32.9) | 49 (33.8) |
| ≥ 256 µg/mL | 7 (10.1) | 1 (1.3) | 8 (5.5) |
| n[a] | 69 | 76 | 145 |
| **MIC of aztreonam for all *PA* isolates (µg/mL)** | | | |
| $MIC_{50}$ | 4 | 2 | 4 |
| $MIC_{90}$ | 128 | 64 | 128 |
| Number of isolates | 128 | 140 | 268 |
| Minimum MIC | ≤ 1 | ≤ 1 | ≤ 1 |
| MIC Maximum | >2048 | 256 | >2048 |
| n[a] | 69 | 76 | 145 |
| **MIC for tobramycin against *PA* for all *PA* isolates (µg/mL)** | | | |
| $MIC_{50}$ | 2 | 2 | - |
| $MIC_{90}$ | 64 | 32 | - |
| Number of isolates | 128 | 140 | - |
| Minimum MIC | ≤ 0.12 | ≤ 0.12 | - |
| MIC Maximum | >1024 | 1024 | - |
| n[a] | 69 | 76 | - |

n[a] = number of patients with available data.

***MO Comments:*** *For Table 007 - E3, the rates of highest aztreonam MIC for PA in sputum were generally balanced across study arms except forMIC ≥ 256 µg/mL where the AI arm has a larger rate than the placebo arm.*

# Demographic Characteristics (Continued)

***Study 005***

Table 005-E1a shows demographic characteristics of study patients in study 005.

**Gender:** there were more males than females in each study arm and within each subgroup except in the placebo TID subgroup which had equal gender distribution. Across study arms, 76/135 (56%) patients who received AI (BID and TID) were male compared to 45/76 (59%) patients who received placebo. In the subgroup that received AI treatment BID, 38/69 (55%) patients were male compared to the placebo BID subgroup which had 26/38 (68%) patients who were male. Thus, there was a higher proportion of male patients in the placebo arm compared to the treatment arm. In the AI TID subgroup, 38/66 (58%) patients were male; 19/38 (50%) were female. There was a higher proportion of male patients in the treatment arm compared to the placebo arm.

**Race:** as expected, as CF is more prevalent among the Caucasian population, the majority of patients were Caucasians. However, there was no significant percentage difference in the distribution of these patients across study arms.

**CF Genotypes:** Considering randomization ratio, the genotypic subtypes were fairly evenly distributed across study arms. Most of the patients in each treatment group and subgroups were homozygous for the ΔF508 mutation. The heterozygous group consisted of patients having the ΔF508 allele and another mutation. They represented 26% in the treatment arms combined and 31% in the placebo arm combined. The remaining patients in each treatment group were classed as unidentified, or other. The Sponsor reported that there were no differences between treatment groups with respect to the sweat chloride test result (mean [SD] for all patients: 102.9 [18.7] mEQ/L).

**Age group:** Most of the patients in the trial were adults. Only a small number of pediatric patients (≥ 6 years to ≤12 age range) participated in the study. In the treatment arm 101/135 (~75%) patients 18 years of age and older received AI compared to 64/76 (84%) patients who received placebo. In the pediatric age bracket ≥ 6 years to ≤ 12 years, 9/135 (6.6%) received AI compared to 1/76 (1.3%) who received placebo treatment. In adolescents >12 to <18 years of age, 25/135 (18.5%) patients received AI treatment compared to 11/76 (14.5%) patients who received placebo.

**Disease Severity:** shown in table 005-E1b. The distribution of patients in the less severe CF category ($FEV_1\% > 50$) versus the more severe category ($FEV_1\% \leq 50$) was broadly in 2:1 ratio.

Thus, 134 /211 (63.5%) patients were in the less severe disease category versus 76/211 (36%) in the more severe disease category.

| Table 005-E1 a | Demographic Characteristics at Day - 42: ITT Population (Sponsors Table 7) for Study 005 | | | | | | |
|---|---|---|---|---|---|---|---|
| Variable | Treatment Groups | | | | | | Total (N = 211) |
| | AI BID (n = 69) | Placebo BID (n = 38 | AI TID (n = 66) | Placebo TID (n = 38) | AI Pooled (n = 135) | Placebo Pooled (n = 76) | |
| **Gender; n (%)** | | | | | | | |
| Male | 38 (55.1) | 26 (68.4) | 38 (57.6) | 19 (50.0) | 76 (56.3) | 45 (59.2) | 121 (57.3) |
| Female | 31 (44.9) | 12 (31.6) | 28 (42.4) | 19 (50.0) | 59 (43.7) | 31 (40.8) | 90 (42.7) |
| **Race; n (%)** | | | | | | | |
| Caucasian | 61 (88.4) | 34 (89.5) | 63 (95.5) | 35 (92.1) | 124 (91.9) | 69 (90.8) | 193 (91.5) |
| African American | 3 (4.3) | 0 | 0 | 0 | 3 (2.2) | 0 | 3 (1.4) |
| Hispanic | 5 (7.2) | 3 (7.9) | 3 (4.5) | 3 (7.9) | 8 (5.9) | 6 (7.9) | 14 (6.6) |
| Other | 0 | 1 (2.6) | 0 | 0 | 0 | 1 (1.3) | 1 (1.5) |
| **Genotype; n (%)** | | | | | | | |
| Homozygous** | 25 (49.0) | 16 (50.0) | 31 (60.8) | 18 (56.3) | 56 (54.9) | 34 (53.1) | 90 (54.2) |
| Heterozygous** | 15 (29.4) | 10 (31.3) | 12 (23.5) | 10 (31.3) | 27 (26.5) | 20 (31.3) | 47 (28.3) |
| Unidentified** | 5 (9.8) | 2 (6.3) | 7 (13.7) | 3 (9.4) | 12 (11.8) | 5 (7.8) | 17 (10.2) |
| Other** | 6 (11.8) | 4 (12.5) | 1 (2.0) | 1 (3.1) | 7 (6.9) | 5 (7.8) | 12 (7.2) |
| **n** | 51 | 32 | 51 | 32 | 102 | 64 | 166 |
| Missing data § | 18 (26.1) | 6 (15.8) | 15 (21.7) | 6 (15.8) | 33 (24.4) | 12 (15.8) | 45 (21.3) |
| **Age group (years); n (%)** | | | | | | | |
| ≥ 6 to ≤12 | 4 (5.8) | 1 (2.6) | 5 (7.6) | 0 | 9 (6.7) | 1 (1.3) | 10 (4.7) |
| >12 to <18 | 13 (18.8) | 7 (18.4) | 12 (18.2) | 4 (10.5) | 25 (18.5) | 11 (14.5) | 36 (17.1) |
| ≥ 18 | 52 (75.4) | 30 (78.9) | 49 (74.2) | 34 (89.5) | 101 (74.8) | 64 (84.2) | 165 (78.2) |
| | | | | | | | |
| **Mean Age (yrs); (SD)** | 26.5 (10.7) | 27.8 (12.0) | 24.1 (9.7) | 28.1(8.8) | 25.3 (10.2) | 27.9 (10.4) | 26.2 (10.4) |

** Denominator = **n** minus missing data; § Denominator = **n**, i.e. # of patients missing in treatment group out of original **n**.

**Table 005-E1b Demographic Characteristics continued – Disease Severity ITT Population for Study 005**

| | *AI BID* | *PLA BID* | *AI TID* | *PLA TID* | *Pooled AI* | *Pooled Placebo* | *Total* |
|---|---|---|---|---|---|---|---|
| *N* | *n = 69* | *n = 38* | *n = 66* | *n= 38* | *n = 135* | *n =76* | *N =211* |
| *$FEV_1$% ≤ 50* | *24 (35%)* | *15 (39.5%)* | *22 (33%)* | *15 (39.5%)* | *46 (34.1%)* | *30 (39.5%)* | *76 (36%)* |
| *$FEV_1$% > 50* | *44 (64%)* | *23 (60.5%)* | *44 (67%)* | *23 (60.5%)* | *88 (65.2%)* | *46 (60.5%)* | *134 (63.5%)* |
| *Other* | *1 (not given)* | *-* | *-* | *-* | *-* | *-* | *-* |

***MO Comments:*** *Overall, the imbalances across treatment arms were probably too small to make any difference in the overall study results. These small imbalances occurred in the gender and age group categories. Gender-wise, the overall proportions of male to female patients between the study arms are comparable (56% in treatment arm versus 59% in placebo arm). Within the subgroups, however, AI BID subgroup had a lower percentage of male patients compared to the placebo BID subgroup (55% versus 68%). There was a higher percentage of male patients in the AI TID subgroup compared to the placebo TID arm (58% versus 50%). There was a higher percentage of pediatric patients within the age bracket ≥ 6 to ≤12 who received AI (6.7%) compared to those who received placebo (1.3%). However, the numbers from which the last percentages were derived are probably too small to be of significance.*

Table 005-E2 enumerates the mean respiratory parameters at Day 0 in study patients. This was after receiving 28 days of TOBI (run-in period). This represented the baseline visit for the patients who would be receiving AI from this time forward for 28 days.
As shown in table 005-EF2a, the mean $FEV_1$ % predicted (and standard deviation) across study arms, were comparable. With respect to CFQ-R scores, the mean CFQ-R respiratory domain scores observed at Day 0 in the placebo TID subgroup were slightly lower than in the AI TID mean subgroup scores. The meann scores in the BID subgroups and even the pooled AI and placebo subgroups are comparable.

**Table 005-E2: (Modified Sponsor's Table 9) Baseline Characteristics at Day 0: ITT Population**

| Variable | Treatment | | | | | |
|---|---|---|---|---|---|---|
| | **AI BID (N = 69)** | **Placebo BID (N = 38)** | **AI TID (N = 66)** | **Placebo TID (N = 38)** | **AI Pooled (N = 135)** | **Placebo Pooled (N = 76)** |
| Mean (SD) $FEV_1$ % predicted | 56.192 (15.628) | 55.655 (17.299) | 57.064 (16.608) | 52.333 (16.258) | 56.618 (16.060) | 53.994 (16.758) |
| Mean (SD) CFQ-R respiratory domain | 63.14 (16.74) | 65.66 (17.39) | 64.23 (18.13) | 58.71 (21.46) | 63.68 (17.38) | 62.14 (19.74) |

## Microbiology

Table 005-E3 shows microbiologic MIC pattern at Day 0. The $MIC_{50}$ of aztreonam for all *PA* isolates was low for each treatment group (≤1, 2, or 4 μg/mL). There was a shift in MIC characteristics, per the Sponsor (not shown), during the 28-day transition period during which patients received TOBI. There had been an upward creep in resistance characteristics among

some of the *Pseudomonas aeruginosa* isolates. The largest change in $MIC_{50}$ from Day -28 to Day 0 occurred in the placebo BID group where the $MIC_{50}$ increased from ≤ 1 µg/mL (Day -28) to 4 µg/mL (Day 0). The maximum MIC identified in the in the AI BID subgroup was >2048 µg/mL compared to 512 µg/mL in the BID placebo arm which probably carried over into the pooled AI MIC data (also >2048 µg/mL) compared to MIC of 1024 µg/mL (one step down) in the pooled placebo group. Otherwise, in other categories in the table, there were generally no significant differences between treatment groups in $MIC_{50}$ or $MIC_{90}$ of aztreonam at Day 0.

**Table 005-E3: (Modified Sponsor's Table 9) Day 0: ITT Population – Microbiology**

| Variable | Treatment | | | | | |
|---|---|---|---|---|---|---|
| | **AI** | **Placebo** | **AI** | **Placebo** | **AI** | **Placebo** |
| | **BID (N = 69)** | **BID (N = 38)** | **TID (N = 66)** | **TID (N = 38)** | **Pooled (N = 135)** | **Pooled (N = 76)** |
| **MIC of aztreonam for all *PA isolates (µg/mL)*** | | | | | | |
| $MIC_{50}$ | 2 | 4 | 2 | ≤1 | 2 | ≤1 |
| $MIC_{90}$ | 64 | 64 | 32 | 64 | 32 | 64 |
| Minimum MIC | ≤1 | ≤1 | ≤1 | ≤1 | ≤1 | ≤1 |
| MIC Maximum | >2048 | 512 | 1024 | 1024 | >2048 | 1024 |
| Number of isolates | 105 | 61 | 111 | 64 | 216 | 125 |

### *6.1.3 Patient Disposition*

## Study 007

Table 007-E4a shows the number of patients screened and their subsequent dispositions. Table 007-E4b shows the number of patients continuing at each visit. As indicated, 253 patients were screened. Of these, 34% failed to meet screening criteria due either to absence of *PA* in their sputum sample or because their $FEV_1$ was > 75% or < 25%.
Two patients randomized to receive AI were withdrawn before receiving trial drug because of receipt of azithromycinin one and the need for additional medications in the second patient. These two patients were excluded from the Safety, ITT, and PP populations.
Of the 164 patients who were randomized and who received trial drug, 124 (76%) patients completed the trial and 40 (24%) patients discontinued. One patient received placebo rather than AI as randomized. For the safety population, the proportion of patients who discontinued in the AI group was 16% vs 32% in the placebo group.

Eleven (13.8%) patients receiving AI discontinued due to AEs versus 23 (27.4%) patients in the placebo group. The most frequent reason for early withdrawal for the safety population was

unrelated AEs. In the placebo group 16 (19%) patients withdrew because of unrelated AEs compared to 8 (10%) patients in the AI group. Pulmonary exacerbations constituted the majority of AEs that led to discontinuation.

**Table 007-E4a (Modified Sponsor's Table 10): Patient Disposition**

| Variable | Patient Disposition: ITT Population for Study 007 | | |
|---|---|---|---|
| | Treatment Groups | | |
| | AI | Placebo | Total |
| | (N = 80) | (N= 84) | (N = 164) |
| № of patients screened | N/A | N/A | 253 |
| № of patients radomized | 83 | 83* | |
| № (%) of patients treated[a] | 80 (100.0) | 84* (100.0) | 164 (100.0) |
| № (%) completing the trial | 67 (83.8) | 57 (67.9) | 124 (75.6) |
| № (%) of patients discontinued | 13 (16.3) | 27 (32.1) | 40 (24.4) |
| **Reasons for early withdrawal** | | | |
| Death | 0 | 0 | 0 |
| Unrelated AE | 8 (10.0) | 16 (19.0) | 24 (14.6) |
| Related AE | 3 (3.8) | 5 (6.0) | 8 (4.9) |
| Trial drug intolerance (AE) | 2 (2.4) | 0 | 2 (1.2) |
| Lost to follow-up | 0 | 1 (1.3) | 1 (0.6) |
| Noncompliance | 0 | 0 | 0 |
| Personal/administrative | 1 (1.2) | 1 (1.3) | 2 (1.2) |
| Other | 3 (3.6) | 0 | 3 (1.8) |

№ = number; [a] Patients treated are those receiving at least part of one dose of trial drug;
N/A: not applicable; * One patient was randomized to receive AI but received placebo.

**Table 007-E4b Number of Patients Continuing at Each Visit: All Patients as Treated**

| Visit | Treatment | | |
|---|---|---|---|
| | AI 75 mg AI (N = 80) n (%) | Placebo (N = 84) n (%) | Total (N = 253) n (%) |
| Screening | N/A | N/A | 253 |
| Day -14 | 80 (100) | 84 (100) | 164 (100) |
| Day 0 | 80 (100) | 84 (100) | 164 (100) |
| Day 14 | 78 (97.5) | 76 (90.5) | 154 (93.9) |
| Day 28 | 73 (91.3) | 65 (77.4) | 138 (84.1) |
| Day 42 | 68 (85.0) | 57 (67.9) | 125 (76.2) |

N/A = not applicable.

***MO Comment:*** *The rate of discontinuation was higher in the placebo arm than in the AI arm. Two (2.4%) in the AI arm did not tolerate trial drug versus none in the placebo arm. The number is small. The Sponsor did not report what "other" represented.*

## Patient Disposition (continued)

**Study 005**
Per Table 005-E5, following the screening process, 247 patients received TSI (or TOBI) starting on Day -28; but 246 (one less patient) were randomized. According to the Sponsor, the 247$^{th}$ patient was withdrawn from the study after receiving TOBI treatment due to a 7.6% decrease in $FEV_1$. The patient required a course of prednisone. The patient was withdrawn by the investigator because he was not at his usual pulmonary baseline. Out of 246 eligible patients randomized, 211 (85.8%) completed TOBI after 28 days of use/treatment. All remaining 211 patients entered the AI/placebo treatment period. Subgroup distributions were as follows: BID = 69 in the AI subgroup versus 38 in the placebo subgroup; TID = 66 in the AI subgroup versus 38 in the placebo subgroup.

**Discontinuations/Withdrawals**
Per tables 005-E5 and 005-E6, of the original 211 randomized patients who received 28 days of TOBI treatment up to Day 0, 90 (42.7%) completed the AI/Placebo trial; 121 (57.3%) were discontinued/withdrawn from the study.
The overall discontinuation rate (after Day 0) was lower in patients who received AI than in those who received placebo (53% versus 66% respectively). Within subgroups, patients who received TID placebo had the highest discontinuation rate (79%). By comparison, among the patients who received AI BID, discontinuation rate was 59%. Within this BID regimen subgroup, AI-treated patients had a lower discontinuation rate (46%) than placebo-treated patients (53%). The discontinuation rates in the AI BID, AI TID, and pooled placebo study patients were 46% (N=69), 59% (N=66) and 66% (N=76) respectively.

Unrelated AEs, per the Sponsor, constituted the most frequent reason for early discontinuation of patients (see Table 005-E5). The incidence of related AEs was higher in patients who received TID regimen (AI TID, 13.6%; Placebo TID, 23.7%). The BID subgroups had lower treatment-related AEs (AI BID, 8.7%; Placebo BID, 10.5 %).

| Table 005-E5 (Sponsor's Table 10): Disposition of Patients: All Patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient Disposition** | **TOBI-treated Patients as Subgrouped To Receive AI/Placebo** | | | | | | **Total (N = 363) n (%)** |
| | **AI** | **Placebo** | **AI** | **Placebo** | **AI** | **Placebo** | |
| | **BID** | BID | TID | TID | Pooled | Pooled | |
| | **(N = 82) n (%)** | **(N = 41) n (%)** | **(N = 82) n (%)** | **(N = 41) n (%)** | **(N = 164) n (%)** | **(N = 82) n (%)** | |
| **Number Screened** | - | - | - | - | - | - | 363 |
| Number Randomized | 82 | 41 | 82 | 41 | 164 | 82 | 246 |
| № treated with TOBI | 82 | 41 | 82 | 41 | 164 | 82 | 247* |
| Dropouts [Not at least one dose of AI/placebo received] | 13 (15.9) | 3 (7.3) | 16 (19.5) | 3 (7.3) | 29 (17.7) | 6 (7.3) | 36* (14.6) |
| № (%) completing TOBI | 69 (84.1) | 38 (92.7) | 66 (80.5) | 38 (92.7) | 135 (82.3) | 76 (92.7) | 211 (85.8) |
| **№ (%) receiving AI/ placebo [Denominator for AI/ Placebo-treatetd patients]** | ↓ **69 (84.1)** | ↓ **38 (92.7)** | ↓ **66 (80.5)** | ↓ **38 (92.7)** | ↓ **135 (82.3)** | ↓ **76 (92.7** | ↓ **211 (85.8)** |
| **Withdrawal after Day 0 ^: Reasons -** | | | | | | | |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unrelated AE | 21 (30.4) | 14 (36.8) | 26 (39.4) | 20 (52.6) | 47 (34.8) | 34 (44.7) | 81 (38.4) |
| Related AE | 6 (8.7) | 4 (10.5) | 9 (13.6) | 9 (23.7) | 15 (11.1) | 13 (17.1) | 28 (13.3) |
| Study drug intolerance | 0 | 0 | 1 (1.5) | 0 | 1 (0.7) | 0 | 1 (0.5) |
| Lost to follow up | 0 | 0 | 0 | 1 (2.6) | 0 | 1 (1.3) | 1 (0.5) |
| Noncompliance | 1 (1.4) | 0 | 1 (1.5) | 0 | 2 (1.5) | 0 | 2 (0.9) |
| Personal/ administrative | 0 | 1 (2.6) | 1 (1.5) | 0 | 1 (0.7) | 1 (1.3) | 2 (0.9) |
| Other | 4 (5.8) | 1 (2.6) | 1 (1.5) | 0 | 5 (3.7) | 1 (1.3) | 6 (2.8) |
| **№ (%) withdrawn** | 32 (46) | 20 (53) | 39 (59) | 30 (79) | 71 (53) | 50 (66) | 121 (57) |
| № (%) completing study§ | 37 (45.1) | 18 (43.9) | 27 (32.9) | 8 (19.5) | 64 (39.0) | 26 (31.7) | 90 (36.4) |

№ = number; AE= Adverse event; ^ = Percentages based on number of patients at Day 0 (211 patients).
§ = Percentages based on number of patients randomized on Day - 28
* = Patient 21208 received TOBI but not randomized; included in the total summary (and safety population) only.

***MO comments:*** *The proportion of dropouts among the AI-treated patients (also after 28 days of treatment) was lower compared to the proportion who received placebo treatment (53% versus 66%). Among subgroups receiving the BID or TID regimen, a higher percentage of dropouts was seen in the placebo-treated than in the AI-treated patients. Using comparable sample sizes, the discontinuation rates in the AI BID, AI TID (subgroups), and pooled placebo (group) study patients were 46% (N=69), 59% (N=66) and 66% (N=76) respectively. There were lower rates of discontinuation in patients receiving AI than those receiving placebo. It was also reported that most patients who withdrew did so due to AEs unrelated to study drug/treatment.*

**Table 005-E6: Number of Randomized ITT Patients Continuing at Each Visit**

| | **Treatment** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **AI** | | | **Placebo** | | | **Total** |
| **Visit** | **BID (N = 69) n (%)** | **TID (N = 66) n (%)** | **Pooled (N = 135) n (%)** | **BID (N = 38 n (%)** | **TID (N = 38) n (%)** | **Pooled (N = 76 n (%)** | **N=211 n (%)** |
| Screening | 69 | 66 | 135 | 38 | 38 | 76 | 211 |
| Day -28 | 69 (100) | 66 (100) | 135 (100) | 38 (100) | 38 (100) | 76 (100) | 211 (100) |
| Day 0 | 69 (100) | 66 (100) | 135 (100) | 38 (100) | 38 (100) | 76 (100) | 211 (100) |
| Day14 | 67 (97.1) | 61 (92.4) | 128 (94.8) | 34 (89.5) | 35 (92.1) | 69 (90.8) | 197 (93.4) |
| Day 28 | 62 (89.9) | 56 (84.8) | 118 (87.4) | 32 (84.2) | 30 (78.9) | 62 (81.6) | 180 (85.3) |
| Day 42 | 58 (84.1) | 44 (66.7) | 102 (75.6) | 26 (68.4) | 25 (65.8) | 51 (67.1) | 153 (72.5) |
| Day 56 | 53 (76.8) | 36 (54.5) | 89 (65.9) | 21 (55.3) | 15 (39.5) | 36 (47.4) | 125 (59.2) |
| Day 70 | 42 (60.9) | 29 (43.9) | 71 (52.6) | 18 (47.4) | 9 (23.7) | 27 (35.5) | 98 (46.4) |
| Day 84 | 37 (53.6) | 27 (40.9) | 64 (47.4) | 18 (47.4) | 8 (21.1) | 26 (34.2) | 90 (42.7) |

***MO comments:*** *The above table shows an accounting (by study visits) of patients as subgroup numbers slowly dwindled with dropouts. According to the dataset submitted by the Sponsor, four of the ninety patients who completed the study needed no antibiotics beyond Day 84 (protocol-specified end of study). Their inclusion was reasonable. Two of the four were in the AI BID subgroup. The other two were in the TID subgroup.*

## Concomitant Medications

***MO Comments:*** *In both studies 007 and 005, each member of the entire study populations received vast numbers of concomitant medications. They included salbutamol, fluticasone propionate with salmeterol dornase, alpha pancreatic enzymes (most commonly pancrelipase), vitamins/multivitamin supplement, ADEKS, antibacterials for systemic use [most commonly azithromycinin (study 005), ciprofloxacin; tobramycin]; drugs for acid related disorders; nasal preparations, mineral supplements, drugs used in Diabetes, drugs for blood and blood forming organ, antihistamines; analgesics; prednisone and some had received influenza vaccine, etc. The rates of use of these medications were generally comparable in all arms of the two pivotal studies. The reviewer believed that further detailed review of the complex cocomitant medications of these patients would bring no added value to this review.*

## Protocol Deviations

The primary efficacy analysis population for each of studies 007 and 005 was the ITT population.
For study 007 the number of patients in the AI arm of the per protocol (PP) population was 74 (92%); the corresponding ITT arm was 80 (100%). In the placebo arm, 71/84 (84.5%) was in the PP population. The reasons for their exclusion included non-compliance with eligibility criteria; not receiving at least 66% of study drug or treated for at least 14 days; use of antipseudomonal antibiotic and attending early termination visit more than 7 days after starting an antipseudomonal antibiotic. In study 005, patients in the pooled AI arm of the PP population constituted 73.8% of the corresponding ITT subgroup while in the placebo arm was 87.8% of the corresponding subgroup. The most common reason for protocol deviation was failure to receive at least 66% of study drug or treatment for at least 7 days. The other deviations were not considered significant by the Sponsor. The reviewer agreed with the Sponsor's assessment.

### *6.1.4 Analyses of Primary Efficacy Endpoints*

**The Efficacy Review Path**
Before getting to the how analyses that were done, the reviewer would first outline the order of presentation of the analyses done.
As indicated in section 5.2 (Review Strategy) and subsection 6.1.1 (Methods), of the three Phase 3 studies submitted by the Sponsor, the pivotal studies 005 and 007were reviewed for efficacy determination of AI for the proposed indication. These two studies were the double-blind, multicenter, randomized, placebo-controlled studies. In study 007, patients received 75 mg TID regimen of AI - the regimen proposed to be marketed. Studies 005 patients received BID and TID regimens. This study (005) was conducted to corroborate study 007. The major differences between the two studies were outlined in subsection 6.1.1.
In ascertaining the efficacy of AI, the order of review presentatioon was as follows:

1. The review of study 007 (primary endpoint evaluation) was presented first, given that this was the study in which study patients received the to-be-marketed regimen (75 mg TID). The primary efficacy endpoint determaination was assessed in patients using a patient reported outcome (PRO) tool, CFQR-R (descibed under section 6.1.1). This instrument was used to assess study patients to ascertain changes (improvement or deterioration) in respiratory symptoms as a measure of treatment benefit or lack thereof, following the receipt of AI versus placebo.

2. Study 005 (primary endpoint evaluation) was presented next so that the primary endpoint evaluation of the regimen to be marketed and that of the supportive study be discussed together under section 6.1.4 [Analysis of Primary Endpoint (s)] of the new CDER clinical template. This was to ascertain the strength of evidence available in the supportive study and whether it was robust enough to support or corroborate study 007 for approval.

3. Study 007 – secondary endpoints (and other endpoints as relevant), to determine consistency with primary endpoint finding.

4. Study 005 – secondary endpoints (and other endpoints as relevant), also to determine consistency with primary endpoint finding. Numbers 3 and 4 were discussed under section 6.1.5 [Analysis of Secondary Endpoint (s)].

The rest of efficacy review followed that pattern in accordance with the the titles and subtitles in the sections and subsections respectively.

## Analyses performed by the reviewer

To verify data integrity and for assurance of data quality, as partly stated in subsection 3.1 of this review, the reviewer took the following steps:

1. A blinded review of a randomly generated patients' Case Report Forms (CRFs) to ascertain the quality of data transcription from such CRFs to the datasets, and to have an assurance that assessment of study patients was acceptable to the reviewer.
2. The Study Endpoint and Labeling Development (SEALD) team was consulted to assess the adequacy of the PRO tool used in the conduct of studies 007 and 005.
3. The Division of Scientific Investigation (DSI) was consulted to investigate for site-specific or investigator-specific problems that could have adverse impact on study results.
4. Worked with the statisticians to perform sensitivity analyses, including an evaluation of outcomes of missing data.
5. Holding multiple discussions with the statisticians also (and upper level management) regarding analysis of study 005 efficacy data.

The SEALD team questioned the CFQ-R PRO tool used in patients assessments in the pivotal phase 3 studies regarding the length of its 2-week recall period which was considered too long for accurate recollection of events. At the time of the review, the issue was not

considered serious enough to make the studies unacceptable. Other than the results of study 005, that was considered not providing adequate coroborative evidence to support study 007, all other analyses processes listed above raised no issues of serious concern.

# Analyses of Primary Efficacy Endpoints - Study 007

Table 007-E5 is the Sponsor's summary table of primary endpoints and their results in study 007. Although patients were assessed at Days 0, 14, 28, and 42 (the last visit) the Sponsor's protocol-specified primary efficacy endpoint in this study was change from Day 0 (baseline) to Day 28 in the clinical symptoms of study patients, as measured by the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R). Primary efficacy endpoint assessments also explored PRO-measured categorical disease severity in form of percentage number of patients who improved or worsened at Day 28 (see table 007-E5).

**The Primary Population [= ITT Population]**
In study 007 protocol, the ITT population served as the primary population. Therefore, the primary efficacy evaluation of AI was based on the performance of the drug as assessed in the ITT study population.

**Minimally Clinically Important Difference (MCID)**
A "Minimally Clinically Important Difference" (MCID) score of 5 had been pre-established in another study to which the Division agreed. This score was the CFQ-R score against which aggregate CFQ-R scores between two pre-specified timepoints were compared. The comparison enabled determination of what score was clinically significant and meaningful to study patients.

**Table 007-E5: Modified Sponsor's Table of Primary Efficacy Endpoints - 007**

| Primary Efficacy Endpoint Results | Result | | | |
|---|---|---|---|---|
| | 75 mg AI TID (N = 80) | Placebo TID (N = 84) | Treat. Diff. | p-value |
| Clinical symptoms as assessed by CFQ-R respiratory domain | | | | |
| Mean (adj) change in CFQ-R respiratory domain score at Day 14 | 7.01 | -0.98 | 7.98 | 0.0006 |
| Mean (adj) change in CFQ-R respiratory domain score at Day 28 | 7.08 | -2.63 | 9.71 | 0.0005 |
| Categorical result: % of patients who improved at Day 28 | 56.3 | 37.3 | - | 0.0055 |
| % of patients who worsened at Day 28 | 25.0 | 44.6 | - | |
| Mean (adj) change in CFQ-R respiratory domain score at Day 42 | 0.62 | -5.71 | 6.33 | 0.0154 |

adj = adjusted; Treat. Diff. = Treatment Difference; - = not applicable.

From the data provided by the Sponsor (table 007-E6), the adjusted mean change in CFQ-R (respiratory domain scores) from Day 0 (baseline) to Day 28, using imputed data, was 7.08 for AI-treated patients and -2.63 for placebo-treated patients. The treatment difference [7.08 – (-2.63)], on Day 28, was 9.71 (p = 0.0005). The change of 9.71, compared to MCID of 5

represented a clinically and statistically significant improvement in respiratory symptoms for AI-treated patients. Although Day 14 assessment was not included in table 007-E6, the treatment difference was 7.01 and was clinically meaningful and statistically significant (p = 0.0006).

Table 007-E6 also provides additional information involving a later time point (Day 42) treatment benefit. Day 42 assessment provided information on whether or not the cumulative clinical benefit gained at Day 28 by study patients was sustained at Day 42. The Sponsor reported that the mean treatment difference at Day 42 had dimished to 6.33 but was still clincally and statistically significant (p = 0.0154).

**Modified Sponsor's Table 15**

| **Table 007-E 6: Actual Change in CFQ-R Respiratory Domain Scores from Day 0 - ITT Population [Imputed Data for Child/Teen/Adult Combined]** | | |
|---|---|---|
| **Time Point** | **Treatment Groups** | |
| | **AI (75 mg TID) (N = 80)** | **Placebo TID (N = 84)** |
| **Day 28** | | |
| n | 80 | 83 |
| Mean (± SD) | 7.88 (18.88) | -1.91 (18.64) |
| Median (range) | 5.56 (-33.3, 66.7) | 0.00 (-44.4, 72.2) |
| Adjusted mean | 7.08 | -2.63 |
| Treatment difference: 75 mg AI – placebo | 9.71 | |
| 95% CI (p-value) | 4.31, 15.11 (p = 0.0005) | |
| **Day 42** | | |
| n | 80 | 83 |
| Mean (± SD) | 1.32 (18.31) | -5.09 (17.02) |
| Median | 0.00 | -5.56 |
| Adjusted mean | 0.62 | -5.71 |
| Treatment difference: 75 mg AI – placebo | 6.33 | |
| 95% CI (p-value) | 1.22, 11.43 (p = 0.0154) | |

CFQ-R respiratory domain scores range from 0 to 100.

***MO Comments:***
*Based on the data in table -007 E 6, the reviewer agrees with the Sponsor that the study has met the primary efficacy endpoint. The change (treatment difference) in CFQ-R (respiratory domain scores) measured in AI-treated patients (9.71), compared to placebo-treated patients (-1.91), on Day 28 was the largest measured in the study and compared to MCID was clinically meaningful to study patients and also statistically significant (p = 0.0005). By Day 42, this treatment difference between the two groups had dwindled from 9.93 to 6.33 although this value at day 42 was also clinically meaningful and statistically significant (p = 0.0154). Therefore, the treatment difference (albeit diminishing which was expected) was sustained for at least another14 days post-treatment. Whether a treatment difference is sustained beyond day 42 could not be determined from this study. Results for the per protocol (PP) population were similar to those of the ITT population as shown in table 007- E7.*

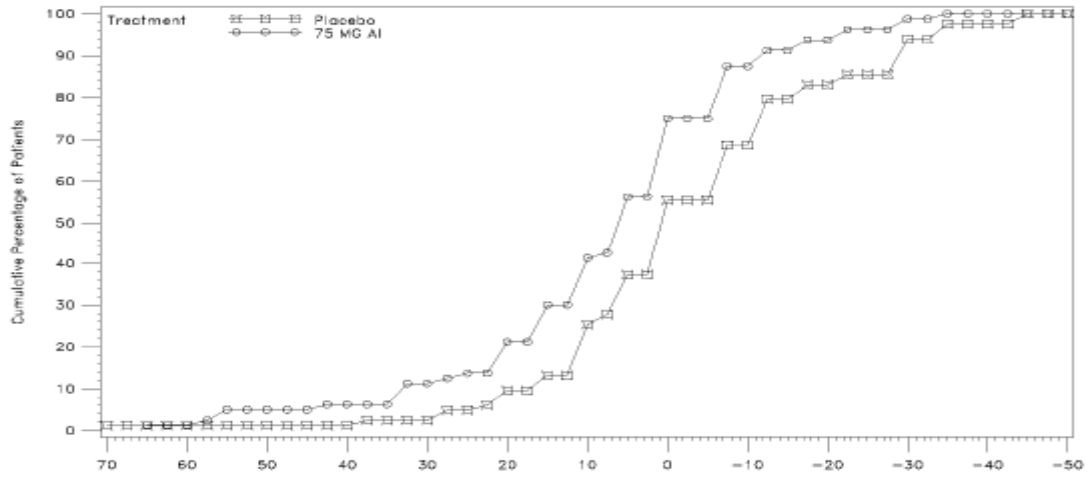
**Per Protocol Population at Day 28 [Imputed Data for Child/Teen/Adult Combined]**

| **Table 007-E7** | | |
|---|---|---|
| **Time Point** | **Treatment Groups** | |
| | **AI (75 mg TID) (N = 80)** | **Placebo TID (N = 84)** |
| | | |
| **Day 28** | | |
| n | 70 | 74 |
| Mean | 8.90 | -0.99 |
| Median | 5.56 | 0.00 |
| Adjusted mean | 8.23 | -1.71 |
| Treatment difference: 75 mg AI – placebo | 9.93 | |
| 95% CI (p-value) | 4.16, 15.71 (p = 0.0009) | |

***MO Comments:*** *If receipt of AI produced such favorable results in the ITT population, one would generally expect that at least comparable or better results would be obtained in the PP population although the converse is not necessarily true. The performance of AI in the PP population shows consistency of study results.*

Figure 007- 1 was provided by the Sponsor and represents cumulative percentage distribution frequency for change in CFQ-R respiratory domain score. The figure illustrates that higher proportions of AI-treated patients reported improvement in symptoms and lower proportions reported deterioration in symptoms than in the placebo-treated group. According to the Sponsor, the observed shift in score of approximately 10 points was considered fairly uniform across the ITT population.

**Figure 007-1: Cumulative Percentage of Patients for Day 28 Respiratory Domain Score Change from Day 0 on Imputed Data for Child/Teen/Adult Combined (ITT Population)**




**CFQ-R respiratory domain scores range from 0 to 100.**

Above figure = Change in Respiratory domain Score from Day 0 to Day 28

**Categorized Change in CFQ-R Respiratory Domain Scores**

Per the Sponsor, change in CFQ-R respiratory domain scores was categorized as improved, stable, or worsened, depending on the magnitude and direction of change in relation to the MCID of ≥ 5. Table 007-E8 is the Sponsor's table modified by the reviewer to show the percentage of patients whose CFQ-R respiratory domain scores demonstrated improvement, no change, or worsening of respiratory symptoms.
There were higher percentages of patients with improvement in respiratory symptoms at Day 28 in the AI treatment group (56%) compared to placebo-treated group (37%) as shown in the Figure 007-2 (Sponsor's figure 5).
The Sponsor explained that, as pre-defined in the statistical analysis plan, this endpoint was tested at a significance level of 0.05. Accordingly, the difference between the treatment groups in categorized change was statistically significant at Day 28 (p = 0.0055). At Day 42, 45% of the patients receiving AI experienced improvement in respiratory symptoms compared to 30% of patients who received placebo (p= 0.0154).

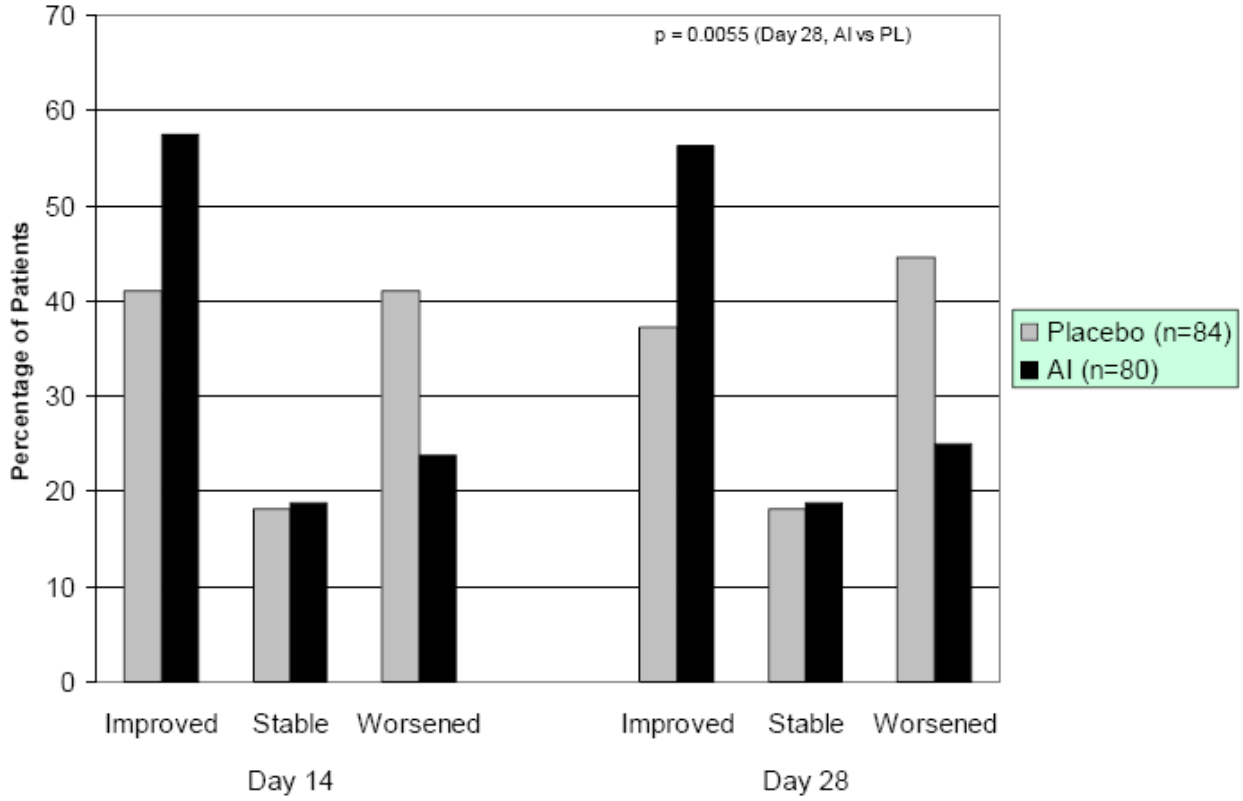
[The results were also similar at Day 14, with 58% of the patients in the AI group experiencing improvement in respiratory symptoms compared to 41% in the placebo group].

**Table-007 E8 (Modified Sponsor's Table 16)**

| **Categorized Change in CFQ-R Respiratory Domain Scores from Day 0 - ITT Population [Imputed Data]** | | |
|---|---|---|
| **Time Point** | **Treatment Groups** | |
| | **AI (75 mg TID) (N = 80)** | **Placebo TID (N = 84)** |
| **Day 14** | | |
| **n[a]** | 80 | 83 |
| Improved - n (%) | 46 (57.5) | 34 (41.0) |
| Stable or no change - n (%) | 15 (18.8) | 15 (18.1) |
| Worsened - n (%) | 19 (23.8) | 34 (41.0) |
| **Day 28** | | |
| **n[a]** | 80 | 83 |
| Improved - n (%) | 45 (56.3) | 31 (37.3) |
| Stable or no change - n (%) | 15 (18.8) | 15 (18.1) |
| Worsened - n (%) | 20 (25.0) | 37 (44.6) |
| P-value[b] | 0.0055 | |
| **Day 42** | | |
| **n[a]** | 80 | 83 |
| Improved - n (%) | 36 (45.0) | 25 (30.1) |
| Stable or no change - n (%) | 15 (18.8) | 15 (18.1) |
| Worsened - n (%) | 29 (36.3) | 43 (51.8) |

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

**Figure 007-2 (Sponsor's Fig. 5): Categorized Change in CFQ-R Respiratory Domain Scores from Day 0 - Day 14 / Day 0 - 28 on Imputed Data (ITT Population)**




***MO comments:*** *As the CFQ-R assessments were performed at Days 0 (baseline), 14, 28, and 42, respondents had to record information based on recall of events of the previous two weeks to report status change. An alternative approach would be to record eventsas they occurred. Information recorded in this manner would be more reliable. Despite this inherent weakness in the use of the PRO tool in study study 007 for patient self assessments, table-007 E8 and figure 007-2 were produced using information gathered from this method of patient-reported assessments. After Day 0, and by Day 14, 57.5% of study patients who received AI had improved compared to 41.0% placebo-treated patients. By Day 28, 56.3% AI-treated patients still remained improved compared to 37.3% of placebo-treated patients. This was statistically significant (p= 0.0055). At Day 28 also, 43.8% of AI-treated patients were either unchanged (18.8%) or clinically worse (25%) compared to placebo-treated patients among whom 62.7% reported clinical statusthat was either unchanged (18.1%) or worse (44.6%). By Day 42 the percentage of improved patients had diminished from 56.3% at Day 28 to 44% in AI-treated group. In placebo-treated patients the the improved cases had dropped from 37.3% on Day 28 to 30.1% on Day 42. There was about a 14% difference between the AI- and placebo-treated groups on Day 42. The indications are that receipt of AI (compared to placebo) made some difference in the respiratory well-being of these CF study patients.*

## Subgroup Analyses of Primary Endpoint for study 007

The Primary Endpoint Subgoup analysis for study 007 was discussed under section 6.1.7 (Subpopulations).

***Primary Efficacy Endpoint Evaluation – Study 005***
This study was designed differently from study 007. The differences in design were highlighted under subsection 6.1.1. Aside from the length of study being longer in study 005 (126 days) than in study 007 (56 days), study patients received TOBI prior to receiving AI or placebo. This was intended to put all patients at the same level at baseline prior to receiving AI or placebo BID or TID. Study 007 patients received no such treatment as they were all going to receive the same dose and regimen (75 mg TID versus placebo TID). Most importantly, the primary efficacy endpoint was to determine how long it took patients receiving AI or placebo to need anti-pseudomonal antibiotics as a result of the development of pre-specified symptoms of pulmonary exacerbation.

**ITT Population**
As in study 007, the ITT population served as the primary efficacy population in study 005. Therfore, the primary efficacy evaluation of AI was based on the performance of the drug in the treatment of ITT study population.

For both studies 005 and 007, the regulatory history indicates that multiple pre-submission interactions and communications occurred between the Division and the Sponsor. Study 005 protocol was amended once. The statistical analysis plan (SAP) for the same was amended twice. For study 007, the protocol was amended twice; the SAP was amended once. According to the Sponsor, the Division agreed *prima facie* to all proposed methods of efficacy data analyses stated in each study protocol and SAP. For study 005, the amended SAP (submitted with thisNDA application) states the following: *"*All efficacy analyses will be conducted on the pooled Al vs pooled placebo treatment groups, followed with pairwise comparisons between Al TID and Al BID vs pooled placebo if the null hypotheses based on pooled data are rejected. If there is a strong suggestion that the two placebo arms are different, they may be analyzed separately as sensitivity analyses."

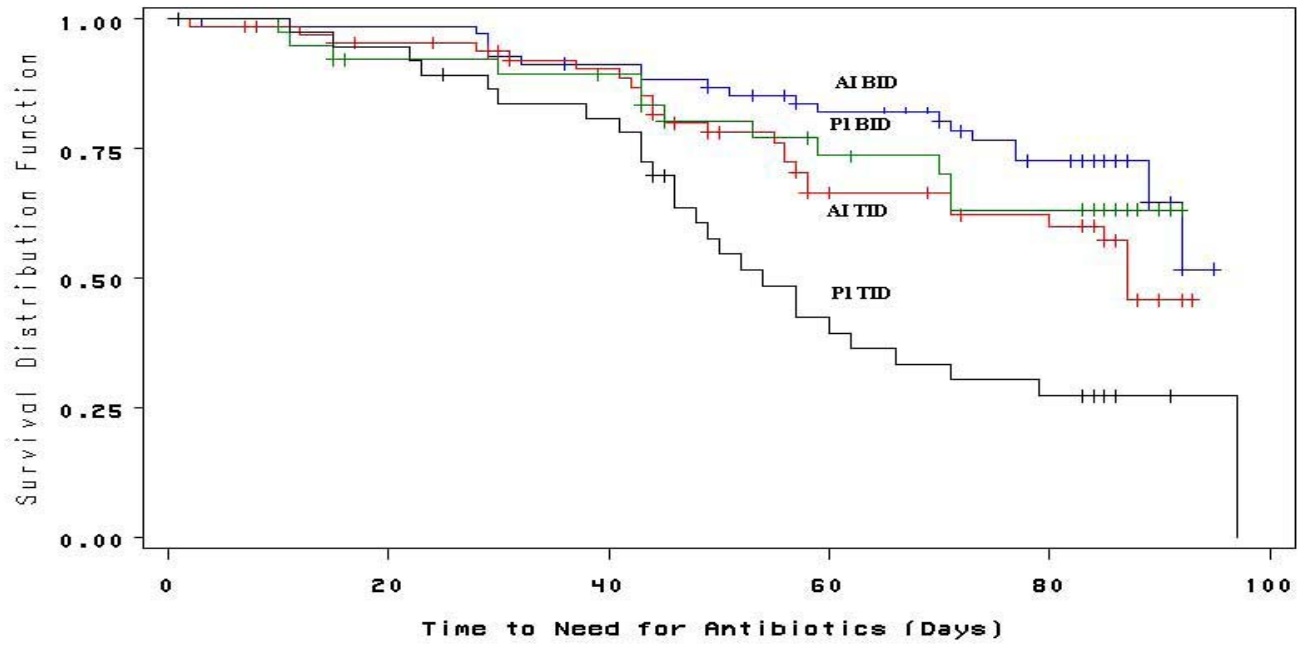
***MO Comments:*** *Despite the above report by the Sponsor regarding the Sponsor-Agency agreement on the approach to data analyses, these agreements were made with no knowledge of how study data would turn out except, perhaps, for expectations based on biological plausibility. For example, as study 005 was designed to have two placebo arms, it would not be unreasonable to expect some consistency in both placebo arms, regardless of the form of regimen received by study patients in the two arms – they were receiving the same, qualitatively identical, placebo. Data obtained from patients who received AI were compared to those from patients who received placebo. As all or most data analyses in this review were essentially these AI-placebo comparisons, validity of such analyses are as good as whether or not the placebo was true, as demonstrated by consistency in both placebo arms . This would influence the overall outcome of study 005 data analyses. The reviewer felt a discussion of the differences in the treatment regimens (BID versus TID) used in study 005 (particularly in relation to the two placebo arms)*

*should precede, and serve as a backgroud to, the primary and secondary efficacy analyses. The divergence of the two placebo arms influenced the reviewer's agreement or disagreement with the Sponsor's data analyses.*

**Regimen Effect**

Figure 1 is a Kaplan-Meier survival curve for the four treatment arms of study 005. It depicts the course of events after patients received study treatment and followed even beyond the nominal end of study, Day 84. Study patients received either AI BID or placebo BID; AI TID or placebo BID.

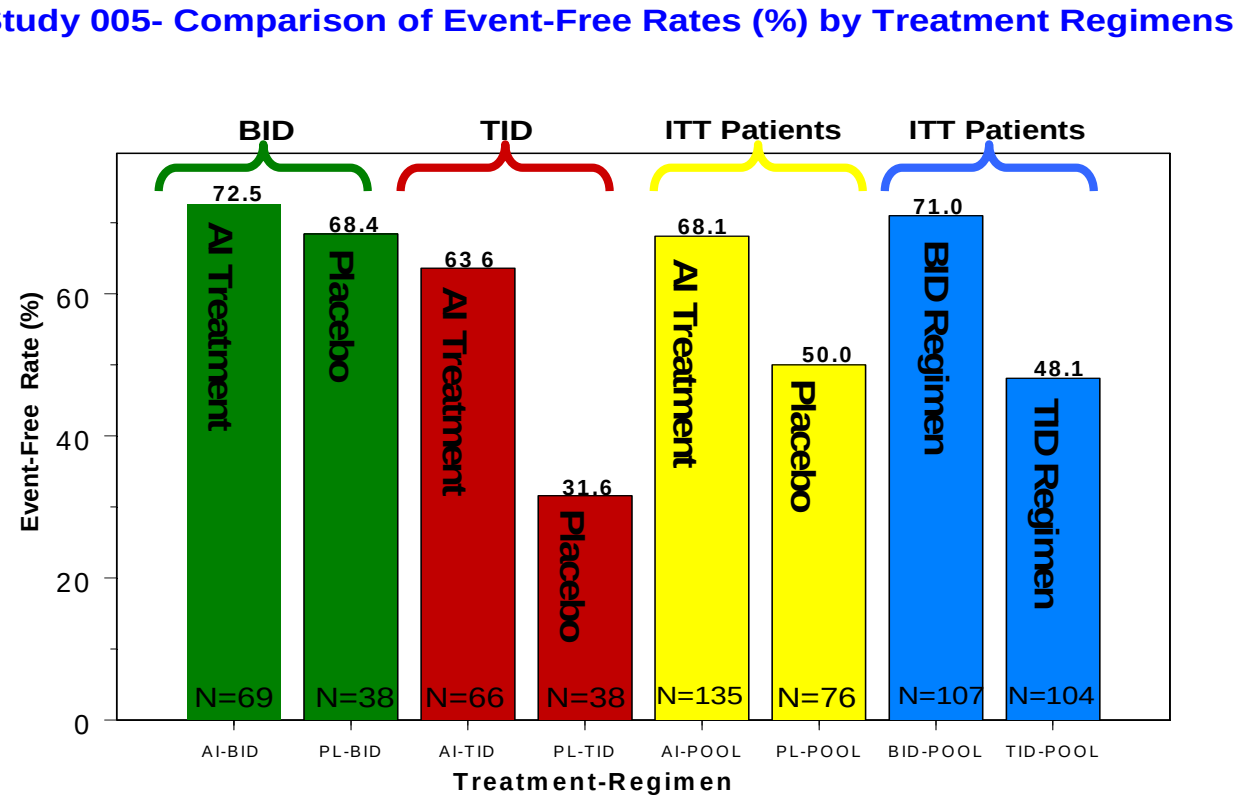
**Figure 005-1: Kaplan-Meier Survival Curve for the Four Subgroup Regimens**




***MO Comments:*** *In figure 005-1, the different arms of the study appeared to be close together in the first 25 to 30 days of the treatment and follow-up periods. They then began to separate rather remain fairly close or almost parallel. By around Day 42, the separation of the placebo TID arm from the other subgroups became more dramatic. On the other hand, patients in the placebo BID arm appeared to be having more beneficial effect than even AI TID study arm patients from aroud Day 60. The BID arms appeared to have performed better than the TID arms. This is further illustrated by the graphs in figure 005-2 where a strong placebo effect is further illustrated by bar graphs created by the statistical reviewer, Dr. Kadoorie.*

*The picture raises a question as to where the true placebo really lies- i.e., is it the placebo BID or placebo TID or pooled placebo? It is unknown. It cannot be determined.*

**Figure 005-2: Event-Free Rates Further Illustrating Strong Regimen Effect**




***MO Comments:*** *The above bar grapgh further illustrates a strong regimen effect. Patients who received placebo BID apparently had higher event-free rates than even patients who received AI TID. It appears that placebo BID was beneficial to a higher rate of study patients than the receipt of AI TID. On the contrary, the receipt of placebo TID was much worse than receiving placebo BID and for that matter, all other treatments. The figure further demonstrates placebo inconsistency.*

**Figure 005- 3: Regimen Effect Data - Wide Separation of Placebo Arms**

## Study 005- Comparison of AI Regimen Effects on Time to Need for Antibiotics (Two-Sided p-values)

| AI → vs. Placebo ↓ | AI BID | AI TID | AI Pooled |
|---|---|---|---|
| Placebo BID | **0.4269** | ***0.5377*** | **0.9240** |
| Placebo TID | *< .0001* | *0.0043* | *<.0001* |
| Placebo Pooled | **0.0019** | **0.1816** | **0.0070** |

***MO Comments:*** *Figure 005 – 3 was also provided by the statistical reviewer, Dr. Kadoorie. It is a crisscross diagram that allows subgroups and pooled data to be compared for regimen effect and significance testing on time to need of antipseudomonal antibiotics based on the data provided by the Sponsor. It further highlights placebo inconsistency. For example, while AI TID vs placebo BID shows a p-value of 1.000, the same AI TID vs placebo TID shows a p-value of 0.0043. And AI TID vs pooled placebo shows a value of 0.1816.*

Table 005-E6 is a modified Sponsor's table showing the post hoc primary efficacy analysis of the regimen effect of study 005 results in the ITT population. The analysis indicated that:

1. Overall, BID regimen showed greater efficacy than TID regimen for both AI and placebo treatments. The Sponsor tested for regimen effect by pooling BID regimen data (i.e., AI BID plus placebo BID) and comparing to TID (i.e., AI TID plus placebo TID). In this comparison, BID was better than TID regimen. The difference was statistically significant (p = 0.0012).

2. The median time to need for anti-pseudomonal antibiotics for predefined symptoms was longer for the placebo BID regimen than for the placebo TID regimen; the difference was significant (p = 0.0043).

3. The median time to need for antipseudomonal antibiotics for predefined symptoms was longer for the BID regimen than for the TID regimen, although not statistically significant (p = 0.0835).

4. The proportions of patients requiring antipseudomonal antibiotics for predefined symptoms were lower for the BID regimens compared to the TID regimens for each treatment [AI: BID = 19/69 (28%) vs TID = 24/66 (36%); placebo: BID = 12/38 (32%) vs TID = 26/38 (68%)]

5. The converse is that the proportions of patients requiring no anti-pseudomonal antibiotics for predefined symptoms were higher for the BID regimens than for the TID regimens for each treatment (AI: 72% BID vs 64% TID; placebo: 68% BID vs 32% TID);

6. In the evaluation of the time to need for inhaled or IV antibiotics for predefined symptoms between the AI BID and placebo BID groups, the difference was not statistically significant (p = 0.4269).

7. However, in stratifying by regimen, the difference in time to need for inhaled or IV antibiotics for predefined symptoms was statistically significant between the pooled placebo and pooled AI groups (p = 0.0067).

**Table 005-E6 (Modified Sponsor's Table 17): Regimen Effect – A Post Hoc Analysis**

| **Time to Needing Antipseudomonal Antibiotics: Regimen Effect → ITT Population** | | |
|---|---|---|
| **parison** | **Event Rate** | **p-value** |
| **Test for regimen effect** | | |
| BID vs TID** | 31/107 vs 50/104 | 0.0012 |
| Placebo BID vs placebo TID | 12/38 vs 26/38 | 0.0043 |
| AI BID vs AI TID | 19/69 vs 24/66 | 0.0835 |
| Pooled AI vs pooled placebo stratified by regimen | 43/135 vs 38/76 | 0.0067 |
| **Test for treatment effect within regimen** | | |
| AI BID vs Placebo BID | 19/69 vs 12/38 | 0.4269 |
| AI TID vs Placebo TID | 24/66 vs 26/38 | 0.0043 |

**Combined placebo and AI BID vs combined placebo and AI TID

***MO Comments:*** *Table 005–E6 displays a) the Sponsor's assessment and comparison of regimen effect of AI and placebo and b) treatment effect within each regimen. From the table (like the Kaplan-Meier Survival Curve described before it), the following are apparent:*

1. *Overall, AI BID regimens appear better than AI TID regimens to different degrees according to what comparison is being made.*
2. *Placebo TID appears to be the worst regimen among the four treatment subgroups.*
3. *The Sponsor's comparison of the treatment difference between Pooled AI vs pooled placebo was stastitstically significant.*

*In the regimen comparison between placebo BID and placebo TID, BID placebo showed better efficacy than TID regimen - based on these data alone. The difference is statistically significant,*

*even though clinically, it is counterintuitive. AI BID appears better in efficacy than AI TID on the curve; however, the difference is not statistically significant. There were only 38 patients in each placebo subgroup. Comparison analysis using small sample sizes can be problematic.*
*Comparison to pooled placebo (even though the regimens used were different – i.e., BID versus TID) increased the number of placebo-treated patients. The fact that the difference between placebo BID and placebo TID subgroups is statistically significant makes it difficult to know the true placebo. The lack of placebo consistency makes any comparison of AI results against that placebo compararator not meaningful.*
*Two letters expressing this concern were sent to the Sponsor on April 22 and 24, 2008. The company responded stating that they believe that the pooled placebo represented the true comparator. In their own words "*Gilead believes the pooled placebo treatment group to be valid for the ascertainment of the true placebo effect for the primary and secondary endpoints."
*The reviewer, like the the rest of the clinical review team, differs with the Sponsor's view on this important point.*

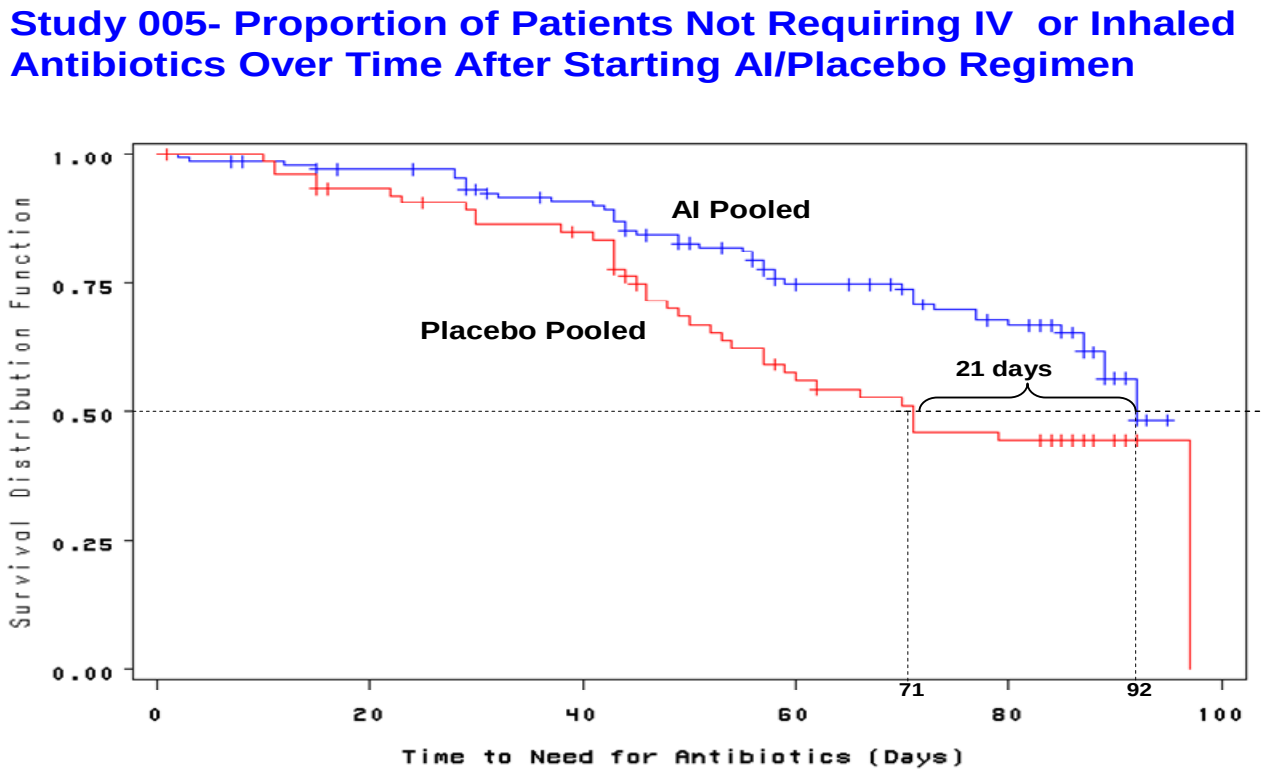
***Primary Efficacy Endpoint Evaluation – Study 005***
Antibiotic (inhaled or administered IV) was considered necessary if patients developed any of the following pre-specified clinical symptoms:

1. Decreased exercise tolerance
2. Increased cough
3. Increased sputum/chest congestion
4. Decreased appetite

In the data analyzed by the Sponsor, the median time to need for inhaled or IV antibiotics by study patients due to development of any of the pre-specified symptoms described above was estimated to be 21 days longer in the pooled AI group than in the pooled placebo group (92 days vs 71 days, p = 0.0070). This is illustrated in Figure 005-2 provided by the Sponsor and modified by the statistician, Dr. Kedoori and the modified Sponsor's table 005-E6. The Sponsor compared pooled AI data to the pooled placebo data for the primary endpoint data analysis. In addition, they compare data from AI BID group with pooled placebo group data. A statistically significant result was obtained (p = 0.0019). However, when AI TID subgroup results were compared to the pooled placebo group, there was no statistically significant difference (0.1816).

According to the Sponsor's analysis of efficacy data, the Kaplan-Meier estimate of treatment failure (i.e., the proportion of patients requiring anti-pseudomonal antibiotics) in the pooled AI treatment group were evaluated and compared to the placebo group. After Day 84 physicians were allowed to initiate prophylactic antibiotic therapy. Beyond that day, no continued uniform follow-up of patients was maintained. Nevertheless, a total of 16 patients (2 in placebo BID, 3 in in placebo TID, 5 in AI BID, 6 in AI TID) were identified as meeting the primary endpoint following a case by case review of the patients. In 11 of these patients their prescriptions for inhaled or IV antibiotics in the two weeks following trial completion or termination were reviewed. The other five were reported as having events on the day they completed the study.

**Figure 005- 2: Proportion of Patients Needing Antibiotics during AI/Placebo treatment and Follow-up Periods**




***MO comments:***
*Figure 005-2 shows the Kaplan-Meier Survival Curve provided by the Sponsor and modified by the stastical reviewer, Dr. Kadoorie. The upper/blue curve represents pooled data of patients who received AI (BID and TID). The lower/red curve represents the pooled data of patients that received placebo (BID and TID). The Sponsor then compared the difference in the median time to need for anti-pseudomonal antibiotics. As shown in the figure, this differnce was 21 days (92 minus 71 days), per the Sponsor's analysis. The difference wass considered to be statistically significant (p=0.0070).*

*Using pooled AI versus pooled placebo data, the delineation of treatment difference between the two treatment groups seems clear. The question is the appropriateness of the pooled data given that the placebo BID and the placebo TID were very different and not comparable. Knowing the true placebo effect is problematic in this assessment. The inclusion of the five patients who had events on the last day of treatment in the ITT analysis population for evaluation was appropriate. The inclusion of the other eleven patients despite the extension of time for needing antibiotics beyond day 84 (last day of study) appears to be appropriate also. The patients apparently did not need anti-pseudomonal antibiotics even after study period and remained availble for evaluation. True and appropriate product primary efficacy outcomes could be ascertained from these patients. Such information could be lost if these patients were right-censored. The longer the*

*period between end of study and when patients had events the more it was helpful to the product if such patients received AI treatment. Such extension of timeto need for anti-pseudomonal antibiotics, in the absence of anything else to explain it, would be considered associated with, or probably attributable to, the receipt of study drug, or placebo, depending on treatment arm of the patients.*

**Table 005-E7 (Modified Sponsor's Table 16): Time (Days) to Need Inhaled or IV Antibiotics due to Pre-defined Symptoms (ITT Population)**

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

**Estimate is outside of the nominal 84-day study period; § = Comparisons are made against pooled placebo; - = not estimable.

## Subgroup Analyses of Primary Endpoint for study 005

Subgroup results were reviewed but due to the concerns related to the primary efficacy analysis, they are not discussed in this review.

### *6.1.5 Analysis of Secondary Endpoints(s) for Study 007*

The key Secondary Efficacy endpoints in study 007 include the following:

1. Mean Percent Change in $FEV_1$ (Liters)
2. Subgroup Analyses of Primary Endpoint
3. Durability of $FEV_1$ Response Following Completion of Treatment with AI
4. $Log_{10}$ *PA* Colony-forming Units in Sputum
5. Use of Antipseudomonal Antibiotics (IV, Inhaled, or Oral) Other than Trial Drug
6. Hospitalization
7. Other secondary endpoints
8. Change in pulmonary function
    - Actual Change in $FEV_1$ Percent Predicted

- AUC Analysis of Change in $FEV_1$ from Day 0 to Day 42
- FVC (L)
- FEF25-75 (L/sec)

9. Change in CFQ-R Nonrespiratory Domains
10. Use of Anti-pseudomonal Antibiotics (IV, Inhaled, or Oral) Other than Trial Drug
    - Change in CF Symptoms and Severity
    - School and/or Work Missed
    - Percent Change in Weight
    - Change in BMI

Table 007-E8 is the Sponsor's summarized key secondary endpoint results from the assessment of patients who participated in study 007. Further discussion of individual endpoint follows the modified Sponsor's tabulated summary.

## Key Secondary Efficacy Analysis

**Table 007-E8– Modified Sponsor's Table of Secondary Efficacy Endpoints &Their Results in Study 007**

| Secondary Efficacy Endpoint Results | Result | | | |
|---|---|---|---|---|
| | **75 mg AI (N = 80)** | **Placebo (N = 84)** | **Treat. Diff.** | **p-value** |
| **Change in pulmonary function** | | | | |
| Mean (adj) percent change in $FEV_1$ at Day 28 | 7.886 | -2.408 | 10.294 | < 0.0001 |
| Mean (adj) percent change in $FEV_1$ at Day 42 | 3.140 | -2.591 | 5.731 | 0.0024 |
| **Change in $log_{10}$ PA CFUs in sputum** | | | | |
| Mean (adj) change in sputum $log_{10}$ PA CFUs at Day 28 | -1.384 | 0.069 | -1.453 | < 0.0001 |
| Mean (adj) change in sputum $log_{10}$ PA CFUs at Day 42 | -0.078 | -0.010 | -0.069 | NS |
| **Use of antispeudomonal antibiotics** | | | | |
| % of patients requiring IV or inhaled antibiotics | 15.0 | 22.6 | - | NS |
| % of patients requiring oral antibiotics | 11.3 | 25.0 | - | 0.0267 |
| % of patients requiring antibiotics overall | 17.5 | 35.7 | - | 0.0131 |
| **Hospitalization** | | | | |
| Number (%) of patients hospitalized at least once between Day 0 and Day 42 | 4 (5.0) | 12 (14.3) | - | 0.0640 |
| Mean number of hospitalization days (Day 0 to Day 42) | 0.5 | 1.5 | - | 0.0487 |
| **Weight** | | | | |
| Mean percent change in weight (kg) at Day 28 | 1.076 | 0.046 | 1.010 | 0.0039 |
| **BMI** | | | | |
| Mean change in BMI (kg/m2) at Day 28 | 0.213 | 0.008 | 0.202 | 0.0054 |

**adj = adjusted; NS = not significant; Treat. Diff. = Treatment Difference; - = not applicable.**

## Change in pulmonary function

### Mean Percent Change in $FEV_1$ (Liters)

The adjusted mean percent change in $FEV_1$ from baseline at Day 28, using imputed data, was 7.9% for AI-treated patients and -2.4% for placebo-treated patients. The treatment difference was 10.3% ($p < 0.0001$). This improvement in respiratory function was a clinically and statistically significant.
At Day 42, the adjusted mean percent change in $FEV_1$ predicted from Day 0 for the AI group was 3.1%, compared with -2.6% for the placebo group. The treatment difference between the AI and placebo groups had decreased to 5.7% but was still statistically significant ($p = 0.0024$). The Sponsor reported that the effect had to do with sustained improvement in the AI group combined with worsening in the placebo group.
According to the Sponsor, the results for the PP population were similar to those of the ITT population.

**Subgroup Analyses for Change in $FEV_1$**

**Effects of Disease Severity**

At Day 28, patients in the more severe disease category [$FEV_1 \leq 50\%$ of predicted; 30 in AI arm and 30 in placebo arm] showed an adjusted mean percent change in $FEV_1$ of 6.3% in the AI arm compared to -4.0% in the placebo arm, as shown in table 007-E9. Patients in the less severe disease category [$FEV_1 > 50\%$ of predicted: 50 in the AI subgroup and 54 in the placebo subgroup] trended toward greater improvement at Day 28 with an adjusted mean percent change in $FEV_1$ of 9.5% in the AI arm and only slight deterioration (-0.6%) in the placebo arm. Results indicated that the adjusted mean percent change in $FEV_1$ for the more severe category was10.3% ($p = 0.0061$), and 10.1% ($p < 0.0001$) in the less severe disease category. In both disease severity categories, the treatment differences between AI and placebo were significant.

The Sponsor reports that results for the PP population were similar to those of the ITT group.

**Table 007-E9. $FEV_1$: Changes in Relation to Disease Severity at Day 28**

| Disease severity category | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| **$FEV_1 \leq 50\%$ predicted** | | | | |
| n | 30 | 30 | | |
| Adjusted mean (%) | 6.3 | -4.0 | 10.3 | = 0.0061 |
| **$FEV_1 > 50\%$ predicted** | | | | |
| n | 50 | 54 | | |
| Adjusted mean (%) | 9.5 | -0.6 | 10.1 | < 0.0001 |

**Effects of Region**

Table 007-E10 shows patterns in $FEV_1$ Changes in Relation to Regions at Day 28.

Patients in the US and Canada [62 in AI arm and 63 in placebo arm] showed an adjusted mean percent change in $FEV_1$ of 6.9% in the AI group compared to -2.2% in the placebo group. The adjusted mean difference was 9% (p = 0.0002).

The adjusted mean percent changes at Day 28 among patients in Australia and New Zealand were 12% in the AI arm and -3.8% in the placebo arm. The adjusted mean difference between AI and placebo groups was 16% (p = 0.0004).
The changes appeared greater for patients in Australia and New Zealand than for patients in the US and Canada but the number of patients assessed in the former region was much smaller.

**Table 007-E10: $FEV_1$ Changes in Relation to Regions at Day 28**

| Region | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| **US and Canada**<br><br>**Changes in $FEV_1$ predicted** | | | | |
| n | 62 | 63 | | |
| Adjusted mean (%) | 6.9 | -2.2 | 9.1 | = 0.0002 |
| **Australia and New Zealand**<br><br>**Changes in $FEV_1$ predicted** | | | | |
| n | 18 | 21 | | |
| Adjusted mean (%) | 12 | -3.8 | 16 | = 0.0004 |

## Effects of Age Subgroups

Table 007-E11 shows $FEV_1$ changes in age group strata at Day 28. Adults aged ≥ 18 years [58 in AI arm and 68 in placebo arm] showed an adjusted mean percent change in $FEV_1$ of 8% in the AI-treated patients compared to -2.4% in the placebo-treated group. The treatment difference between the two groups was 11% (p < 0.0001)

For patients aged < 18 years [21 in AI arm and 16 in placebo arm], the adjusted mean percent change in $FEV_1$ was 7.5% in the AI-treated patients and -2.9% in the placebo-trerated patients at Day 28. The difference between the two groups was 10% (p = 0.0790). This was not statistically significant. The Sponsor explains this as being probably due to the small sample size.

**Table 007-E11 $FEV_1$ Changes in Age Group Strata at Day 28**

| Age subgroup | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Age ≥ 18 years**<br><br>**$FEV_1$ predicted** | | | | |
| n | 58 | 68 | | |
| Adjusted mean (%) | 8 | -2.4 | 9.1 | < 0.0001 |
| **Age < 18 years**<br><br>**$FEV_1$ predicted** | | | | |
| n | 21 | 16 | | |
| Adjusted mean (%) | 7.5 | -2.9 | 16 | = 0.0790 |

## Effects of Gender

The changes in $FEV_1$, as shown in table 007-E12, were slightly greater in males than in female patients. For males [48 receiving AI and 45, placebo], adjusted mean change at Day 28 was 9% in the AI-treated patients and -2.3% in those receiving placebo. The treatment difference was 11% (p = 0.0003). Also at Day 28, the female patients [32 received AI and 39, placebo] showed an adjusted mean percent change in $FEV_1$ of 5.8% in those who received AI compared to -2.7% in those who received placebo. The difference between AI and placebo subgroups within the female poplulation was 8.5% (p = 0.0035) which was statistically significant.

**Table 007-E12 $FEV_1$ Changes in Gender Subgroups at Day 28**

| Gender subgroup | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| **Male Patients**<br><br>**$FEV_1$ predicted** | | | | |
| n | 48 | 45 | | |
| Adjusted mean (%) | 9 | -2.3 | 11 | = 0.0003 |
| **Female Patients**<br><br>**$FEV_1$ predicted** | | | | |
| n | 32 | 39 | | |
| Adjusted mean (%) | 5.8 | -2.7 | 8.5 | = 0.0035 |

## Durability of $FEV_1$ Response Following Completion of Treatment with AI

Table 007-E13 displays changes in $FEV_1$ percent predicted as assessed at Day 28 and Day 42. Per the Sponsor, among the patients treated with AI, some of the improvement in $FEV_1$ seen at Day 28 was sustained at Day 42. The adjusted mean percent change in $FEV_1$ from Day 0 to Day 28 was 8.9% (n = 75) for patients receiving AI compared to 4.6% at Day 42 (n = 72). Also at Day 42, adjusted mean percent change in $FEV_1$ for placebo-treated patients was -0.7%). Thus, the treatment difference between the two treatment groups at Day 42 was 5.3%. It was statistically significant (p = 0.0130).

**Table 007-E13. Durability of $FEV_1$ Response Following Completion of Treatment with AI**

| $FEV_1$ predicted | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Day 28 Visit** | | | | |
| n | 75 | 75 | | |
| Adjusted mean (%) | 8.87 | -1. 840 | 10.7 | < 0.0001 |
| **Day 42 Visit**<br><br>**$FEV_1$ predicted** | | | | |
| n | 72 | 61 | | |
| Adjusted mean (%) | 4.58 | - 0.71 | 5.3 | = 0.0130 |

## Effects of Highest Aztreonam MIC at Day 0

There was no notable effect of highest aztreonam MIC on percent change in $FEV_1$. Patients with isolates whose highest aztreonam MIC was ≤ 8 μg/mL at Day 0 [38 were AI-treated and 50 placebo-treated] had an adjusted mean percent change in $FEV_1$ at Day 28 of 9% in AI-treated patients compared to -2.7% in placebo-treated patients. Treatment difference was12% and was statistically significant (p = 0.0002).

The changes at Day 28, as table 007-E14 shows, were similar for patients with isolates whose highest baseline aztreonam MIC was > 8 μg/mL (31 in AI subgroup and 26 in placebo subgroup). The adjusted mean change was 8% in AI-treated patients versus -3.0% in those who received placebo. The treatment difference was 11% and was also statistically significant (p = 0.0030).

A similar pattern was observed at Day 14, although there was slight improvement in the placebo group for both aztreonam MIC subgroups rather than the deterioration seen at Day 28.

**Table 007-E14:. Effects of Highest Aztreonam MIC at Day 0 (Imputed Data)**

| Change | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| ***MIC* ≤ 8 μg/mL**<br><br>**$FEV_1$ predicted** | | | | |
| n | 38 | 50 | | |
| Adjusted mean (%) | 9 | -2.7 | 12 | = 0.0002 |
| ***MIC* > 8 μg/mL**<br><br>**$FEV_1$ predicted** | | | | |
| n | 31 | 26 | | |
| Adjusted mean (%) | 8 | -3.00 | 11 | = 0.0030 |

### $Log_{10}$ *PA* Colony-forming Units in Sputum

According to the Sponsor, and as shown on table 007-E15, at baseline (Day 0), the mean $log_{10}$ *PA* colony forming unit (CFU) sputum density values were similar in the AI and placebo groups. In the AI group, $log_{10}$ *PA* CFUs sputum density had decreased by more than 1.5 $log_{10}$ *PA* CFUs at

Day 28. The $log_{10}$ *PA* CFUs in the placebo-treated group remained near baseline values at Day 28. At Day 42, $log_{10}$ *PA* CFUs s had returned to near baseline values in both the AI and placebo groups.

**Table 007-E15. Mean (± SD) $Log_{10}$ *PA* CFUs in Sputum (ITT Population)**

| Timepoint | AI TID (N = 80) | Plaebo TID (N = 84) |
|---|---|---|
| **Day 0** | | |
| n | 62 | 74 |
| Mean (SD) | 6.574 (2.000) | 6.273 (2.081) |
| **Day 28** | | |
| n | 64 | 66 |
| Mean (± SD) change | 5.027 (2.564) | 6.096 (2.234) |
| **Day 42** | | |
| n | 59 | 50 |
| Mean (± SD) change | 6.352 (2.057) | 6.171 (1.763) |

## Change in Sputum $Log_{10}$ *PA* CFUs from Day 0 (ITT Population)

Table 007-E16 displays changes in sputum $Log_{10}$ *PA* CFUs from Day 0 following the receipt of AI/placebo by study patients.

From Day 0 to Day 28, adjusted mean $Log_{10}$ *PA* CFUs sputum density decreased (improved) by 1.384 in the AI group and increased (worsened) by 0.069 in the placebo group. The difference between the AI and placebo groups for change in $Log_{10}$ *PA* CFUs in sputum at Day 28 was -1.453 and was statistically significant ($p < 0.0001$). At Day 42 there was no statistically significant difference between the AI and placebo groups for change in $Log_{10}$ *PA* CFUs in sputum. The treatment difference was -0.069 ($p = 0.8218$).

**Table 007-E16. Change in Sputum $Log_{10}$ *PA* CFUs from Day 0 (ITT Population)**

| Timepoint | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| **Day 28** | | | | |
| n | 53 | 61 | | |
| Mean (± SD) change | -1.476 (2.540) | -0.025 (0.786) | | |
| Adjusted mean | -1.384 | 0.069 | -1.453 | < 0.0001 |
| **Day 42** | | | | |
| n | 50 | 49 | | |
| Mean (± SD) change | -0.193 (1.375) | -0.118 (1.724) | | |
| Adjusted mean | -0.078 | -0.010 | - 0.069 | 0.8218 |

## Use of Anti-pseudomonal Antibiotics (IV or Inhaled) Other than Trial Drug

Twelve patients (15%) in the AI group used IV or inhaled antipseudomonal antibiotics compared to 19/84 (23%) in the placebo group. However, this difference was not statistically significant ($p = 0.2364$).

**Hospitalization**

Table 007-E17 displays the characteristics of hospitalization. The majority of patients hospitalized between Days 0 and 42 (2/4 and 9/12 for the AI and placebo groups, respectively), were hospitalized after their last treatment dose.The Sponsor defined hospitalization as the formal admittance of a patient into a hospital for any medical reason for more than one calendar day. Hospitalization parameters included:

- the cause of hospitalization;
- the proportion of patients hospitalized and
- the number and percent of days hospitalized.

Pulmonary exacerbation was the predominant cause of hospitalization in both treatment groups between Day 0 and Day 42 (AI group →2; placebo group→8). Other reasons for hospitalizations included hemoptysis (1 placebo patient only; bowel obstruction (one patient in AI group), chest pain (1 patient in AI group), and cellulitis of left foot (1 patient also in AI group). Overall, of the patients hospitalized during this period, 4/80 (5.0%) were from the AI-treated group compared to 12/84 (14%) of the the placebo arm (p = 0.0640). Although the rate of hospitalization was less in the AI-treated group, the difference was not statistically significant.

In addition to fewer hospitalizations inpatients who received AI vs those who received placebo, the following benefits were also reported:

- the mean number of hospitalization days was lower for AI group vs placebo group, i.e., 0.5 days vs 1.5 days, respectively (p = 0.0487).
- The percent of days hospitalized was also lower in the AI group (1.3%) than in the placebo group (3.6%).

These hospitalizations were categorized as SAEs in all of the patients.

**Table 007-E17: Hospitalization between Day 0 and Day 42 (ITT Population)**

| | AI TID (N = 80) | Plaebo TID (N = 84) |
|---|---|---|
| | | |
| Percent of days hospitalized | 1.3 | 3.6 |
| Number of patients not hospitalized - n (%) | 65 (81.3) | 56 (66.7) |
| Number of patients withdrawn and not hospitalized - n (%) | 11 (13.8) | 16 (19.0) |
| Number of patients hospitalized at least once - n (%) | 4 (5.0) | 12 (14.3) |
| Number of patients hospitalized after Day 42 - n (%) | 1 (1.3) | 0 |
| Total number of patients hospitalized - n (%) | 5 (6.3) | 12 (14.3) |
| Total number of hospitalizations | 5 | 14[b] |
| **Cause of hospitalization**[a] | | |
| Lower respiratory - n (%) | 2 (2.5) | 9 (10.7) |
| Upper respiratory - n (%) | 0 | 0 |
| Gastrointestinal - n (%) | 1 (1.3) | 1 (1.2) |
| Other - n (%)[a] in $FEV_1$ | 1 (1.3) | 2 (2.4) |
| | | |
| Number of hospitalizations | 4 | 12 |
| **Number of hospitalization days** | | |
| Mean (± SD) | 0.5 (2.6) | 1.5 (4.0) |
| Median | 0 | 0 |
| Minimum | 0 | 0 |
| Maximum | 17 | 18 |
| | | |

[a] A patient is counted once within each cause but may be counted in more than one cause.
[b] One patient (Patient 39739) was hospitalized three times.

***MO Comments:*** *Supportive evidence of efficacy of AI gathered from secondary endpoint results may include prevention of hospitalization, or, if hospitalized, a reduction in the length of hospital stay. As shown in the table above, 4/80 (5.0%) patients who received AI were hospitalized compared to 12/84 (14.5%) placebo-treated patients. Although the difference was not statistically significant, the slight difference is noteworthy because of the disease involved. In some other less severe, less chronic disease diseases, perhaps, the difference and the number of patients involved might be considered small and inconsequential. In CF, if prevention of hospitalization is achieved for a relatively small number of patients, that is important. More so when other benefits go together with it as reported by the Sponsor. They include:*

- *the mean number of hospitalization days, which was lower for patients in the AI group than in the placebo group (0.5 days vs 1.5 days, respectively, p = 0.0487).*
- *the percent of days hospitalized which was also lower in the AI group (1.3%) than in the placebo group (3.6%)*

## Other Secondary Efficacy Endpoints

### FVC [Liter(s)]

As shown in table 007-E18, the AI group had a mean (adjusted) improvement of 0.112 L in their forced vital capacities [FVC (L)] while the placebo group showed a mean (adjusted) deterioration of -0.090 L. The actual change in FVC from Day 0 through Day 28 between patients in the AI group and those in the placebo group was 0.201 L (p = 0.0163). The difference was ststistically significant.

At Day 42, per the sponsor, the difference between the AI and placebo groups was not (clinically) significant.

**Table 007-E18: [Modified Sponsors's Table 26] Actual Change in FVC (L): from Day 0 Imputed Data (ITT Population).**

| Time period | AI TID (N = 80) | Plaebo TID (N = 84) | Treatment Differnce | p-value |
|---|---|---|---|---|
| **(Day 0 to Day 28)** | | | | |
| Mean (± SD) change | 0.129 (0.331) | -0.071 (0.690) | | |
| Adjusted mean | 0.112 | -0.090 | 0.201 | = 0.0163 |
| **Day 0 to Day 42 Percent Change** | | | | |
| Mean (± SD) change | 0.036 (0.306) | -0.096 (0.681) | | |
| Adjusted mean | 0.021 | -0.112 | 0.133 | = 0.1005 |

Per the Sponsor → Pretreatment measurements at Day 0, Day 14, and Day 28 were used in the calculations.

### $FEF_{25-75}$ (L/sec)

The actual change in $FEF_{25-75}$ from Day 0 though Day 28 between patients in the AI group and those in the placebo group (median difference) was 0.160 L/sec ($p < 0.0001$). This was statistically significant (see table 007-E19). At Day 42, the median treatment difference between the AI and placebo groups was 0.080 L/ second ($p < 0.0026$). This was still significant although smaller in magnitude. The results for actual change in $FEF_{25-75}$ seemed to have maintained consistency with the results for mean percent change in $FEV_1$.
At Day 14, the median difference between these groups was also significant (0.140 L/sec, $p < 0.0001$) and similar in magnitude to Day 28.

**Table 007-E19: Modified Sponsors's Table 27**

| **Actual Change in $FEF_{25-75}$ (L/sec) from Day 0 on Imputed Data: ITT Population** | | | | |
|---|---|---|---|---|
| **Timepoint** | **AI TID (N = 80)** | **Plaebo TID (N = 84)** | **Median Differnce** | **p-value** |
| **Day 28** | | | | |
| Median | 0.080 | -0.030 | | |
| Minimum | -1.48 | -1.19 | | |
| Maximum | 1.86 | 0.78 | | |
| | | | 0.160 | <0.0001 |
| **Day 42** | | | | |
| Median | 0.030 | -0.020 | | |
| Minimum | -0.47 | -1.36 | | |
| Maximum | 1.65 | 2.07 | | |
| | | | 0.080 | = 0.0026 |

Pretreatment measurements at Day 0, Day 14, and Day 28 were used in the calculations.

## Change in CFQ-R Nonrespiratory Domains

Although respiratory functioning was central to the entire well-being of the CF patients, other parts of the whole person, i.e. how the individual patient felt, functioned and survived was also evaluated. In this regard, Selected Nonrespiratory Domain Scores of the CFQ-R were assessed.

In the assessment of physical functioning, for example, the mean score at baseline for AI-treated patients was 66.9 versus 62.4 in placebo-treated patients. The difference was 4.5. The Day 28 mean score for AI-treated and placebo-treated patients were 70.8 and and 58.4 respectively. The difference was 12.4. It was considered statistically significant. Using median scores, the Sponsor also reported that improvements in some other non-respiratory domains and that statistically significant differences between AI-treated and placebo-treated patients in these areas were noted in the patients' vitality, emotional functioning, eating disturbances, and health perception.

There were no statistically statistically significant difference between the groups for change at Day 28 (nonparametric ANCOVA) in the following areas: social functioning, body image, role limitations/school performance, weight disturbance, and digestion.

**Use of Antipseudomonal Antibiotics (IV, Inhaled, or Oral) Other than Trial Drug**

Overall, 14/80 (18%) patients in the AI group used antipseudomonal antibiotics compared to 30/84 (36%) in the placebo group. The difference between the treatment groups was statistically significant (p = 0.0131). Among the subset of patients who used oral antipseudomonal antibiotics, 9/80 (11%) patients were in the AI treatment arm compared to 21/84 (25%) patients in the placebo group. This difference between the treatment groups also was statistically significant (p = 0.0267).

## Change in CF Symptoms and Severity

Table 007-E20 displays numbers (and percentages) of patients reporting changes in their symptom severity, according to the system organ class (SOC).

At each visit, patients were questioned by their physician about changes in their CF symptoms (eg, cough, sputum production, etc) since the last visit. Responses were categorized as follows: worsened, unchanged, or improved. Symptoms were categorized by SOC and preferred term. The percentage of patients who reported improvements in these symptoms to their physicians was similar in the AI and placebo treatment groups at Day 28.

**Table 007-E20: Change in CF Symptom Severity (by SOC) from Day 0 to Day 28[a] (ITT Population) [Modified Sponsors's Table 29]**

| System Organ Class | Treatment | |
|---|---|---|
| | AI 75 mg (N = 80) n (%) | Placebo (N = 84) n (%) |
| **Gastrointestinal disorders** | | |
| Worsened | 4 (5.0) | 3 (3.6) |
| Unchanged | 18 (22.5) | 7 (8.3) |
| Improved | 4 (5.0) | 1 (1.2) |
| **General disorders and administration site conditions** | | |
| Worsened | 1 (1.3) | 5 (6.0) |
| Unchanged | 5 (6.3) | 5 (6.0) |
| Improved | 6 (7.5) | 1 (1.2) |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Worsened | 13 (16.3) | 19 (22.6) |
| Unchanged | 47 (58.8) | 36 (42.9) |
| Improved | 10 (12.5) | 9 (10.7) |

**SOC = System Organ Class**

***MO Comments:*** *Although there are higher rates of improvement reported in patients who received AI compared to those who received placebo (particularly in the gastrointestinal and general disorders/administrative site disorder categories), the numbers involved are small. In addition, a lower rate of patients in the AI arm than in the placebo arm reported worsened symptoms in the respiratory, thoracic and mediastinal disorder category. All other symptom changes were comparable across study arms.*

## School and/or Work Missed

Per the Sponsor, there were no differences between treatment groups in the number of school/work days missed or the percent of patients who missed school/work at least once.

## Change in Patient's Ability to Produce Sputum

The Sponsor also reported that there were no differences between treatment groups in the change in patient's ability to produce sputum at Day 14 and Day 28.

## Percent Change in Weight

There was a significant difference (see table 007-E 21) between the AI and placebo groups for percent change in weight at Day 28 (1.0%, p = 0.0039), with patients in the AI group showing greater adjusted mean weight gain (1.1%) than those in the placebo group (0.1%). A similar pattern was seen at Day 14.

**Table 007-E21: (Modified Sponsor's Table 30) Percent Change in Weight (kg) from Day 0 (ITT Population)**

| Timepoint | Treatment | |
|---|---|---|
| | **75 mg AI (N = 80)** | **Placebo (N = 84)** |
| **Day 14** | | |
| n | 80 | 84 |
| Mean (± SD) | 0.791 (1.584) | 0.103 (1.954) |
| Median | 0.606 | 0.000 |
| Adjusted mean | 0.790 | 0.109 |
| Treatment difference: 75 mg AI – placebo | 0.682 | |
| 95% CI (p-value) | 0.129, 1.234 (p = 0.0160) | |
| **Day 28** | | |
| n | 76 | 76 |
| Mean (± SD) | 1.076 (2.200) | 0.046 (2.021) |
| Median | 0.879 | 0.000 |
| Adjusted mean | 1.085 | 0.074 |
| Treatment difference: 75 mg AI – placebo | 1.010 | |
| 95% CI (p-value) | 0.330, 1.691 (p = 0.0039) | |

## Change in BMI

Table 007-E22 shows changes in BMI measures in AI-treated and placebo-treated patients during Day 28 (as well as Day 14) assessment. According to the Sponsor, the adjusted mean BMI in patients who received AI was 0.213 $kg/m^2$ compared to 0.011 $kg/m^2$ obtained in the placebo-treated patients. The treatment difference was 0.202 and was statistically significant (p = 0.0054). There were significant differences between the AI and placebo groups for change in BMI also at Day 14.

**Table 007-E22: (Modified Sponsor's Table 31) Actual Change in BMI ($kg/m^2$) from Day 0: ITT Population**

| Timepoint | Treatment | |
|---|---|---|
| | 75 mg AI (N = 80) | Placebo (N = 84) |
| **Day 14** | | |
| n | 80 | 84 |
| Mean (± SD) | 0.161 (0.319) | 0.030 (0.414) |
| Median | 0.142 | 0.000 |
| Adjusted mean | 0.163 | 0.029 |
| Treatment difference: 75 mg AI – placebo | 0.134 | |
| 95% CI (p-value) | 0.019, 0.250 (p = 0.0224) | |
| **Day 28** | | |
| n | 76 | 76 |
| Mean (± SD) | 0.213 (0.431) | 0.008 (0.443) |
| Median | 0.178 | 0.000 |
| Adjusted mean | 0.213 | 0.011 |
| Treatment difference: 75 mg AI – placebo | 0.202 | |
| 95% CI (p-value) | 0.061, 0.344 (p = 0.0054) | |

### *6.1.5 Analysis of Secondary Endpoints(s) for Study 005*

**Study 005:**

For study 005, the secondary efficacy endpoints were as follows:

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

Table 005-E8 provides a tabulated summary of results of key secondary endpoits for study 005. Results for individual secondary endpoints are discussed briefly following this table.

**Table 005-E8 (Sponsor's study 005 Synopsis Table): Clinical symptoms as assessed by CFQ-R respiratory domain [Summary of Key Secondary Endpoints Evaluated]**

| Key Secondary Endpoint Assessed | Result | | | |
|---|---|---|---|---|
| | **Pooled** AI (N = 135) | **Pooled** Placebo (N = 76) | **Treat. Diff.** | **p-value** |
| 1. Mean change in CFQ-R respiratory domain score at Day 28 | 4.34 | -0.66 | 5.01 | 0.0196 |
| Categorical result: % of patients who improved at Day 28[a] | 51.5 | 37.0 | NA | 0.0289 |
| % of patients who worsened at Day 28[a] | 28.0 | 38.4 | NA | |
| 2. Change in pulmonary function - Mean percent change in $FEV_1$ at Day 28[b] | 3.9 | -2.4 | 6.3 | 0.0012 |
| 3. Hospitalization[c] Number (%) of patients hospitalized at least once during trial | 14 (10.4) | 3 (3.9) | NA | NS |
| 4. Weight Median percent change in weight at Day 28 | 0.38 | -0.17 | 0.66 | 0.0377 |
| 5. BMI Mean change in BMI ($kg/m^2$) at Day 28 | 0.066 | -0.108 | 0.174 | 0.0362 |
| 6. Change in CF symptoms and severity % of patients showing improvement in respiratory, thoracic and mediastinal disorders SOC CF symptoms at Day 28 | 12 | 1 | NA | NA |
| 7. Change in $log_{10}$ *PA* CFUs in sputum Mean change in sputum $log_{10}$ PA CFUs at Day 28[d] | -0.434 | 0.225 | -0.659 | 0.0059 |

Notes: NA= not applicable; NS = not significant; Treat. Diff. = Treatment Difference.
[a] A greater % of patients improved (had an increase in score of >5) in the AI BID group than in the AI TID group (55% vs 48%, Day 28).
[b] There was no apparent dose response for $FEV_1$.
[c] Number of hospitalizations was low. There were no treatment differences in time to first hospitalization. Respiratory symptoms were the main cause of hospitalization: 11/14 patients (AI) vs 3/3 patients (placebo). Of the 11 AI-treated patients with respiratory hospitalizations, 7 occurred after Day 28.
[d] The mean reduction in $log_{10}$ CFU at Day 14 was lower in the AI BID than in the AI TID group (- 0.184 vs -0.753), indicating CFU reduction occurred more quickly in the AI TID group than in the AI BID group. However, the decrease from Day 0 in mean $log_{10}$ *PA* CFUs was similar for the two AI groups at Day 28 (-0.489 vs -0.373 for the AI BID and TID groups, respectively).

***MO Comments:*** *Table 005–E8 shows the Sponsor's tabulation results of selected secondary endpoints assessed during study 005. As has been discussed in this review (section 6, under "Reviewer's comments on study 005"), analyzing study 005 results have been problematic primarily because, the data appear unreliable. As already stated, as the study was designed to evaluate BID and TID regimens in the same study, patients were to receive TOBI for 28 days at the end of which they were to be randomized to AI or placebo arms BID or TID. The goal was to put patients at comparable levels at the threshold of receving AI or placebo. The Sponsor, however, randomized the patients before receiving TOBI. As patients may have responded to TOBI to different degrees, there could have been some dissimilarities in*

*patients' lung status at the beginning of 28 days of AI or placebo (i.e., at baseline). There was no chance to randomized patients to allow neutralization of what ever (residual) imbalances may have been present following the receipt of TOBI. At the end, there was a pronounced regimen effect. Even placebo BID patients showed a higher "efficacy" rate than AI TID patients. BID placebo and TID placebo arms were divergent. At the end of the day, the true placebo response could not be determined. The data became uninterpretable.*

*In light of this, despite the relatively extensive review of Study 005 data thus far, the reviewer considers analysis of additional secondary endpoints as no longer helpful or useful to the review.*

### *6.1.6 Other Endpoints*

Not applicable.

## *6.1.7 Subpopulations*

## Subgroup Analyses of Primary Endpoint – Study 007

Subgroup analyses for the primary endpoint (CFQ-R respiratory domain scores) were performed to examine patient responses to treatment with AI (versus placebo) in specific subpopulations. The effect of AI (versus placebo) treatment in the following subgroups were evaluated.

**Effects of Disease Severity**

Under this subgroup, per the Sponsor, the stratification of the disease by severity put study patients into two severity groups: those with $FEV_1 \leq 50\%$ predicted and those with $FEV_1 > 50\%$ predicted, as shown in table 007-E9. More patients were in the latter category (randomized into AI = 50 and, placebo = 53) than in the former (AI subgroup = 30; placebo = 30).

At Day 28, patients with $FEV_1 \leq 50\%$ predicted showed a treatment difference between groups for change in the CFQ-R (respiratory domain) score of 8.25. This was not statistically significant [p = 0.0839]. The treatment difference between groups among patients in the less severe disease category ($FEV_1 > 50\%$ predicted) was 10.90 and was statistically significant (p =0.0018).

The Sponsor also presented results obtained at Day 14 where there was no difference between the treatment groups (p = 0.3105) for the subgroup of patients with $FEV_1 \leq 50\%$ predicted, but for those with $FEV_1 > 50\%$ predicted, there appeared to be greater percentages of patients with improvement in the AI group than in the placebo group (66% vs 42%, respectively – p = 0.0003).

In the PP population at Day 28, the results were consistent with results obtained in the ITT population. Day 42 data were not provided by the Sponsor.

| Table-007 SP1: Categorized Change in CFQ-R Respiratory Domain Scores from Day 0 - ITT Population [Imputed Data for Child/Teen/Adult Combined] | | | | |
|---|---|---|---|---|
| | $FEV_1 \leq 50\%$ predicted | | $FEV_1 > 50\%$ predicted | |
| **Time Point** | **AI (75 mg TID) n (%)** | **Placebo TID n (%)** | **AI (75 mg TID) n (%)** | **Placebo TID n (%)** |
| **Day 14** | | | | |
| **N** | 30 | 30 | 50 | 54 |
| N | 30 | 30 | 50 | 53 |
| Mean (± SD) | 3.70 (18.53) | -1.94 (13.55) | 10.22 (14.20) | 0.68 (16.29) |
| Adjusted mean | 2.93 | -1.17 | 10.60 | 0.32 |
| Treat diff→75 mg AI – placebo | 4.10 | | 10.28 | |
| 95% CI (p-value) | -3.92, 12.12 (p = 0.3105) | | 4.80, 15.76 (p = 0.0003) | |
| **Day 28** | | | | |
| **N** | 30 | 30 | 50 | 54 |
| N | 30 | 30 | 50 | 53 |
| Mean (± SD) | 4.91 (21.01) | -4.72 (15.63) | 9.67 (17.46) | -0.31 (20.11) |
| Adjusted mean | 4.22 | -4.03 | 10.14 | -0.76 |
| Treat diff→75 mg AI – placebo | 8.25 | | 10.90 | |
| 95% CI (p-value) | -1.14, 17.64 (0.0839) | | 4.16, 17.64 (p = 0.0018) | |

***MO Comments:*** *The study had a smaller number of patients in the more severe category of lung disease (*$FEV_1 \leq 50\%$ *predicted) than in the less severe category (*$FEV_1 > 50\%$ *predicted). In general, patients with more severe disease might be expected to have more room for improvement. However, the data show more modest improvement at day 14 in patients with greater disease severity.*

For discussion of the subgroups that follow, refer to table 007- E10.

**Effects of Region**
At Day 28, the 124 patients from the US and Canada (AI–treated = 62; placebo-treated = 62) showed an adjusted mean change in CFQ-R respiratory domain score of 5.89 for AI and -1.47 for placebo-treated patients. The treatment difference was 7.36 (p = 0.0223).

Thirty nine patients were studied in Australia and New Zealand (18 received AI; 21 placebo). The changes in these patients appeared better than those from US and Canada. At Day 28, AI-treated and placebo-treated patients had adjusted mean changes of 11.65 and -5.64 respectively. Treatment difference was 17.29 (p-value = 0.0037).

**Effects of Age Group**
Per the Sponsor, overall, there was a greater improvement in the CFQ-R respiratory domain scores for younger patients (< 18 years) than for older ones (≥ 18 years). At Day 28, 126 patients aged ≥ 18 years (59 receiving AI and 67 placebo) showed an adjusted mean change of 4.82 after receiving AI compared to -1.53 following receipt of placebo. The CFQ-R respiratory domain scores gave a treatment difference of 6.35 (p = 0.0495). In 37 patients aged < 18 years (with 21

in the AI arm and 16 in the placebo group), adjusted mean changes were 12.73 in the AI-treated patients and -6.19 in placebo-treated patients. The treatment difference was 18.91 (p = 0.0006).

**Effects of Gender**
At Day 28, females (n = 71: AI →32 and placebo→39) showed a mean (± SD) change in CFQ-R respiratory domain score of 10.76 (± 22.25) for those receiving AI compared to -0.43 (± 22.16) for female patients receiving placebo. The difference between AI and placebo in the arithmetic means was similar for males (n = 92: AI → 48 and placebo→44); mean (± SD) change was 5.96.

**Table 007- SP2. Subgroup Analyses**

| **Categorized Change in CFQ-R Respiratory Domain Scores at Day 28 - ITT Population [Imputed Data for Child/Teen/Adult Combined]** | | | | |
|---|---|---|---|---|
| | **Treatment Groups** | | | |
| | **AI TID** | **Placebo TID** | **Treatment Diff.** | **P-value** |
| **Effects of Region (Day 28)** | | | | |
| **U.S. and Canada** | | | | |
| **N** | 62 | 62 | | |
| Adjusted mean | 5.89 | -1.47 | 7.36 | 0.0223 |
| | | | | |
| **Australia & New Zealand** | | | | |
| **N** | 18 | 21 | | |
| Adjusted mean | 11.65 | -5.64 | 17.29 | 0.0037 |
| **Effects of Age Group (Day 28)** | | | | |
| ≥ 18 | | | | |
| **N** | 59 | 67 | | |
| Adjusted mean | 4.82 | -1.53 | 6.35 | 0.0495 |
| < 18 | | | | |
| **N** | 21 | 16 | | |
| Adjusted mean | 12.73 | -6.19 | 18.92 | 0.0006 |
| **Effects of Gender (Day 28)** | | | | |
| **Male** | | | | |
| **N** | 48 | 44 | | |
| Mean (±SD) | 5.96 (±16.23) | -3.22 (±14.99) | 9.18 | |
| **Female** | | | | |
| **N** | 32 | 39 | | |
| Mean (±SD) | 10.76 (±22.25) | -0.43 (±22.16) | 11.19 | |

***MO comments:*** *The reviewer agrees with the analysis of the primary efficacy endpoints of study 007 by the Sponsor. The study results have met the efficacy endpoint as specified in the study protocol. The one piece of information the reviewer would have liked to see is how much longer beyond day 42 the treatment effect was sustained. The reviewer acknowledges the fact that Day 56 was not part of the protocol.*

### *6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations*

Not applicable.

### *6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects*

Not applicable.

### *6.1.10 Additional Efficacy Issues/Analyses*

No additional efficacy issues beyond the discussions under efficacy summary (section 6).

# Efficacy Conclusion

The efficacy conclusion has also been provided under "Efficacy Summary" (section 6 of this review). Briefly, the Sponsor submitted two pivotal Phase 3, well-controlled, blinded, multicenter studies for review to assess the efficacy (and as part of safety) of AI for approval.

The efficacy review has been completed. Study 007 provided adequate data. Following a review of the data, the MO's came to the conclusion there was strong evidence to establish the efficacy of AI. The data derived from study 005, however, did not amount to adequate evidence to support the efficacy findings provided by study 007results to permit approval of AI. As a result, and based on efficacy data reviewed, the NDA (# 50814) is approvable.

The Sponsor will need to return for futher discussion of plans to conduct another study that could provide data to support study 007 results for possible approval of AI in the future.

# 7. Review of Safety

# Safety Summary

NDA # 50814 was submitted as a 505 (b)(2) application. Accordingly, aside from relying on the the studies submitted to the NDA by the Sponsor for safety information, the reviewer was also to rely on the previous findings of safety (and efficacy) of aztreonam (azactam®) for approval of AI. The Sponsor also provided some literature references as an additional source of safety information to determine the safety profile of AI.

The reviewer relied on the studies conducted by the Sponsor as the major source of safety information for AI. There were 537 AI-treated subjects and patients in the database. Of these, 519 were CF patients. Eighteen were healthy adults who received AI in the Sponsor's initial Phase 1 study (study 001). As shown in table S2, the Sponsor conducted 3 Phase 3 studies, one Phase 2 study, and 2 Phase 1 studies for this application. Two of the Phase 3 studies (studies 007 and 005) were double-blind, multicenter, placebo-controlled studies. The other Phase 3 study

was an open-label follow-on study comprising 151 and 56 (total, 207) patients enrolled from studies 005 and 007, respectively. In the follow-on program, patients received multiple courses of AI. The follow-on study (006) was to serve primarily to expand the safety database of AI. In all three studies, patients generally received 75 mg TID or BID of AI (or placebo). Study 005 included TID or BID treatment arms while study 007 included TID arms only. In study 006, patients received AI TID or BID according to the arm to which they were originally randomized in either study 005 or 007. There was no placebo arm in study 006.
In study 003 (their Phase 2 study), a three-arm study, patients received 225 mg BID, 75 mg BID or placebo BID for 14 days. The highest dose received by any study participant (285 mg) was in study 001 and was received by one of the healthy adults.

## Safety Conclusions

After reviewing the safety results, and based on the analyses of the data submitted for review, the MO has reached the following safety conclusions:

1. Among all study subjects and patients who received AI, one death occurred. Due to complications of the underlying illness and the multiple concomitant medications the patient was receiving, attribution of death to the receipt of AI could not be made; the death did not appear to be causally related to the receipt of AI.

2. For patients who received TID treatments, serious adverse events (SAEs) were reported at generally low rates across the two study arms. Cough and productive cough were the most common SAEs. These SAEs were mostly reported at rates that were either comparable across study arms or at higher rates in the placebo arm than in the AI arm. In the BID arms, patients who reported SAEs did so in small numbers that precluded meaningful comparisons of frequency rates. The only patient whose SAE was considered treatment-related received placebo treatment.

3. Drug-related or study procedure-related AEs leading to discontinuation from the study occurred at higher rates in the placebo arms than in the AI arms (whether BID or TID).

4. In all Phase 3 studies, cough and productive cough were consistently the two most frequently reported all causality AEs, both reported at at rates >30.0% in all study arms during the treatment period. However, the frequency rates among the patients who received AI treatment were similar to placebo rates in studies 007 and 005.

5. In all Phase 3 studies also, cough remained the most frequently reported treatment – realated AE. It was reported at a higher frequency rate among AI-treated patients who received TID regimen than in patients who received placebo treatment (17.1% vs 8.2% respectively). Among patients who received the BID regimen, who were also smaller in number, the frequency rates were comparable in the two treatment arms (17.4% vs 18.4%).

**Laboratory Data**

6. In the two pivotal studies, the rates of development of hematologic abnormalities (leukocytosis, leukopenia, eosinophilia, anemia and thrombocytopenia) were all comparable although some of the numbers were so small that comparisons were not meaningful). There were no treatment-related hematologic abnormalities reported.

7. In the blinded controlled studies, most cases of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were less than 3 times the upper limit of normal (ULN). Most patients who had ALT/AST elevation > 3 times ULN did have such elevations at sceening or baseline. Only one patient who was receiving 75 mg AI TID had outlier ALT/AST elevations at 10x – 20x ULN in study 006 which was discovered during visit 8. The levels on visit 7 and visit 9 were normal. The enzyme levels normalized by the patient's next visit 28 days later. No explanation was provided by the Sponsor for the event. No case met Hy's Law.

8. The rates of hyperglycemia were comparable among patients who received AI and placebo (TID or BID). Two cases had hypoglycemia < 40 mg/ dL, one each in the AI TID and placebo BID arm.

**Vital Signs**

9. With regards to vital signs, the rate of recorded temperatures (Axillary/ Oral) $\geq 100.4\ ^0$F ($38^0$C) in patients who received AI TID was higher than the rate in patients who received placebo TID (4.1% vs 0%). The rate of assigning fever as an AE was correspondingly higher in patients who received AI TID than in patients who received placebo TID (being 13.0% vs 9.8% respectively). The other vital sign comparisons in the pivotal study patients were generally similar across study arms.

**Other**

10. No dose related development of AEs was apparent in the submitted studies. With respect to the assessment of duration-related benefit of AI, based on the open-label study 006 data after patients had received up to six cycles of AI, the Sponsor has suggested that 75 mg TID has efficacy advantage over 75 mg BID regimen over such several cycles of AI treatment.

## 7.1 Methods

### *7.1.1 Clinical Studies Used to Evaluate Safety*

Table S1 (a miniature but modified version of Table G2 under subsection 5.1), shows a listing of clinical studies that provided the bulk of safety data upon which the safety evaluation of AI was based. The one Phase 2 and 3 Phase 3 studies contributed most of the safety information evaluated.

| Table S1 | **Clinical Studies Used to Evaluate Safety** | |
|---|---|---|
| **Studies Phase** | **Study Protocols** | **Study Description** |
| 3 | Study 007 | Double-blind Phase 3 studies |
| | Study 005 | |
| | Study 006 | Open-label Phase 3 study |
| 2 | Study 003 | Double-blind Phase 2 study |
| 1 | Study 002 | Phase 1 studies |
| | Study 001 | |

### *7.1.2 Adequacy of Data*

Table S2 shows the entire clinical study database. Altogether, 537 study subjects and patients received AI in the drug development program. Of this number, 519/537 (97%) were CF patients while 18/537 (3%) were healthy adults in Phase 1. There were 422 CF patients in the Phase 3 part of the program. In the 2 double-blind pivotal studies, 215/537 (40%) received AI (75 mg BID and TID). The open label Phase 3 study patients were 207/537 (39%) of the database. The double-blind Phase 2 study contributed 74/537 (14%) of the database. Phase 1 patients comprised 74/537 (8%) of the database.

The highest dose received by any study participant was 285 mg by six healthy adults. The highest by any CF patients was 225 mg. The longest duration patients received AI was 28 days per cycle of treatment. In studies 007 and 005, study patients received one cycle of AI treatment; some patients in study 006 had received six to seven cycles of treatment and this open-label study was still on-going at the time of submission of this NDA.

***MO comment:*** *The AI development program comprised 519 CF patients who received the study product. Given the finite number of CF patients worldwide (60,000 – 65,000), particularly in the U.S. (32,000 – 35,000) where most of study patients were enrolled, the database is acceptable.*

*The reviewer considers the data amassed from the various studies for this review to be adequate - quantitatively and qualitatively. Given the peculiarity of the study population in terms of the rarity (and nature) of their disease, an assessment of the quantitative adequacy of the database must be tempered with this reality. The task of finding 519 CF patients for enrollment into a clinical study can be arduous. Accordingly, a safety database ≥ 500 is generally considered adequate, barring any AE of significance whose further exploration and charaterization were precluded by a relatively meager database. In the absence of any suspicion of such caliber of AE in this review, this database was considered adequate and allowed detection of common adverse adverse events in this finite special population.*

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**Table S2: Safety Database: Aztreonam Inhalational Aerosol (AI) Development Program**

| Number of Patients / Subjects who received AI | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Grand Total (N) = 537 (CF patients = 519)** | | | **Regimen** | | | | |
| | | | **BID (n = 151)** | | | **TID (n = 271)** | |
| **Phase** | **Study** | | **Number** | **Dose** | | **Number** | **Dose** |
| **3** | | **Phase 3 Database: n = 422** | | **75 mg** | | **n = 271** | **75 mg** |
| | **007** | | **n = 0** | | | **n = 80** | **√** |
| | **006** | | **n = 82** | **√** | | **n = 125** | **√** |
| | **005** | | **n = 69** | **√** | | **n = 66** | **√** |
| | | | | | | | |
| **2** | **003** | **Phase 2 Database: n = 74** | **n = 37** | **75 mg** | | | |
| | | | **n = 37** | **225 mg** | | | |
| | | | | | | | |
| **1** | | **Phase 1 Database: n = 41** | | **Doses received (mg)** | | **Patients/ Subjects** | |
| | **002** | | **n = 23** | **75 →150 →225** | | **CF patients** | |
| | **001** | | **n = 18** | **95 (n=6) →190 (n=6) →285 (n=6)** | | **Healthy adults** | |

**√ = Same dose as above**

### *7.1.3 Pooling Data across Studies to Estimate and Compare Incidence*

Data were pooled across studies and reviewed to compare incidence of AEs as follows:

- Data from the 2 Phase 3 double-blind studies (study-007 and the TID arms of study-005) were pooled together for ascertainment of AE rates between the AI arm and the placebo arm; the BID arms of study 005 were evaluated to ascertain if the BID regimen effect seen in efficacy part of the review was also manifested in study patients with regards to incidence of AE reports relative to AI TID or placebo TID arm.

- The Phase 2 study (study 003) was also double-blinded. However, unlike the Phase 3 studies where patients received 28 days of AI (at 75 mg BID or TID), study 003 patients received AI for 14 days - 75 mg BID in one arm, and 225 mg in the other. There was also a third (placebo) arm. For this reasons, study 003 was reviewed separately to explore for potential dose- and duration-related AEs.

- The open-label Phase 3 study (study 006) was reviewed separately;

- The 2 Phase 1 studies, also, were reviewed for possible significant AEs.

- Literature materials submitted were screened for additional useful/relevant AE information.

## 7.2 Adequacy of Safety Assessments

### *7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations*

Regarding overall exposure and demographics of target populations, in section 7.1.2 ("Adequacy of Data") the doses of AI administered to study participants (from Phase 1 through Phase 3), and regimens used, and the duration for which study patients received AI were discussed. In the efficacy portion of the review, the various demographic subpopulations exposed to AI were also discussed as part of the primary endpoint analysis of studies 007 and 005 (section 6.1.7). Secondary endpoints of the two study results were also analyzed.
The dose of 75 mg was selected for use in study patients and was administered BID or TID. The Sponsor then selected 75 mg TID as the to-be-marketed dose, should the product be approved. The dose seems appropriate based on the rationale underlying the selection. How the dose was selected for use in study patients is further described in the next subsection (7.2.2) below. The selection seemed based more on the optimal effective dose (beyond which no additional benefit to patient was demonstrable) than the concern about development of dose-associated AEs, which was relatively small compared to 75 mg BID, but more respectable compared to the placebo arm, (see study 003, table 7S3 under treament-related AE), although the denominator numbers, particularly placebo number, were small.
The duration of use per cycle (28 days) also seems appropriate. Lessons learned from the Sponsor's Phase 2 study where patients received 75 mg or 225 mg or placebo BID for 14 days included preliminary indication of potential inferiority of product efficacy at 14 days compared

to 28 days course per cycle. The longer term duration of use (multiple cycles) was explored in study 006.

Product was used in CF patients of various demographic characteristics – age (in pediatric and adult patients); gender (in male and female patients); in patients with various degrees of severity of illness (in patients with $FEV_1 \leq 50\%$ predicted and $FEV_1 > 50\%$ predicted); in varying regions (North America, Australia and New Zealand); etc. These demographic subgroups were represented in relative reasonable proportions in the studies submitted in the NDA application.

In eliciting safety information, the Sponsor/investigators appeared to have done their due diligence in the assessment of study patients during adverse events detemination. Patients seemed adequately clinically assessed. Vital signs findings were properly determined. Laboratory testing seemed reasonable and scientifically applicable. Potentially important laboratory findings seemed adequately explored. With some exceptions in some patients with liver enzyme elevations, high laboratory values seemed mostly appropriately followed.

### 7.2.2 Explorations for Dose Response

Please refer to Dr. Sarah Robertson's review for full description of the Sponsor's data on dose-response exploration. Pertinent to this section of the review is the information from 2 studies. Part of the review of study 002 data indicated that "… sputum concentrations in adult CF patients appeared to increase approximately proportional to dose from 75 mg to 150 mg at all timepoints assessed. However, from 150 mg to 225 mg, there is only a minimal increase in sputum concentrations (~ 12%)". In adolescent CF patients, however, their sputum concentrations did "…not appear to increase with increasing dose…" This information, per Dr. Robertson, should be tempered by the considerable variability seen in sputum concentrations in this adolescent cohort.

It was also reported that sputum data from CF patients and the plasma data from healthy subjects suggested that beyond 150-190 mg, the mechanism for local AI pulmonary deposition and, possibly, pulmonary absorption, appeared saturated. Doses beyond these levels, apparently, were no longer pharmacologically additive or clinically beneficial.

Dose relationship to drug product safety was explored in the Sponsor's placebo-controlled Phase 2 study which, in addition to the placebo arm, had two other AI arms: 75 mg and 225 mg.

### *7.2.3 Special Animal and/or In Vitro Testing*

Dr. Amy Ellis evaluated the Sponsor's preclinical pharmacology/toxicology submission.
In the animal studies conducted by the Sponsor, Sprague-Dawley rats received nebulized AI or vehicle (30 mM NaCl in water) daily for 104 weeks via nose-only inhalation.
Estimated achieved inhaled daily doses were 0, 31, 56, and 120 mg/kg/day (expressed in terms of free aztreonam). Estimated pulmonary deposited doses would be 10% of the estimated achieved inhaled doses. Pertinent (drug-related) findings included:

**Respiratory tract**

- Eosinophilic globules in the nasal cavity;
- Minimal to mild atrophy of the olfactory epithelium; and
- Minimal to mild rhinitis.

In a two-year rat carcinogenicity study, the pertinent findings were as follows:

- No increased mortality
- Increase in thyroid C-cell adenomas in female rats observed in high doses (achieved inhaled dose estimated to be 120 mg/kg/day).

Accordingly, the sponsor considered the results seen in the thyroid gland positive findings for tumorigenicity in high dose female rats and proposed to mention these C-cell adenomas in the label. The Peto trend analysis met the Executive Carcinogenicity Assessment Commitee (ECAC)'s stated criterion for a statistically significant increase in a common tumor type ($p<0.005$). However, neither the Peto nor the Fisher analyses met the Committee's criterion for pairwise comparisons ($p<0.001$).

Of note, per Dr. Ellis, there were similar findings in rats in the studies conducted for the review of TOBI NDA (# 50,753). The findings were not considered significant enough to be reported, let alone highlighted, in the product label.

Therefore, following their meeting held on June 12, 2008, ECAC concluded their assessment with the following statements regarding the two-year rat carcinogenicity findings:

- *The Committee agreed that the study was adequate.*
- *The Committee has also concluded that the study was negative for drug related tumors and recommended that the Cayston™ label reflect the absence of drug-related findings.*

### *7.2.4 Routine Clinical Testing*

### *7.2.5 Metabolic, Clearance, and Interaction Workup*

Per Dr. Sarah Robertson's review, about 7% of intravenously administered aztreonam is metabolized in the liver by hydrolytic splitting of the beta-lactam ring. Aztreonam was reported relatively resistant to oxidative metabolism in human pulmonary and hepatic microsomes. But the metabolism of aztreonam in the lungs has not been adequately elucidated.

Systemically, AI is excreted by glomerular filtration and tubular secretion. It is reported that ≈ 60-65% of IV aztreonam in CF patients is excreted in the urine unchanged. Wheareas, in healthy volunteers, approximately 10% of the total AI dose was recovered in the urine in a 24-hour collection period. Lower urinary recovery of AI is probably related to the much slower absorption of aztreonam (from slow pulmonary transit) relative to aztreonam administered intravenously.

### *7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class*

Aztreonam is considered a unique beta-lactam antibiotic and is the only monobactam of clinical significance developed so far. The potential AEs for similar drugs in the larger beta-lactam antibiotics are listed under section 2.4. However, one purpose of aerosol delivery of AI is to reduce systemic exposure and related systemic adverse effects. None of the related beta-lactam antibiotics have been developed for aerosol delivery.

## 7.3 Major Safety Results

**Definitions of Adverse Events (AEs) and Serious Adverse Events (SAEs)**

In all the studies conducted for this review, an **event** included any side effect, injury, toxicity, sensitivity reaction, intercurrent illness, or sudden death. An **adverse event (AE**) comprised any adverse experience (whether or not it was considered drug-related), that occurred after the onset of study drug administration to a subject or a patient. A **serious adverse event (SAE)** consisted of any AE that was life-threatening or resulted in any of the following outcomes: death, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly, or birth defect. AEs that did not meet at least 1 criterion for an SAE were considered non-serious. However, an important medical event that did not meet the SAE criteria may have been considered an SAE if, based upon appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes mentioned.

Serious adverse events were reviewed, including examination of SAEs that could have represented lack of drug efficacy. SAE rates were determined by treatment group for specific subgroups of interest. Relationship of SAEs to study drug was ascertained and described as related, unrelated, unlikely related, possibly related, or probably related.

**An Overview of Adverse Events**

**Studies 003, 005, and 007 Patients**
Table S3 displays an overview of the numbers (and percentages) of patients in the double-blind placebo-controlled studies 003, 005 and 007 (and 006) patients who reported at least an event (AE or SAE) or was discontinued from study following the receipt of AI/placebo during the studies.
**Death:** There was no death in these double-blind placebo-controlled studies.

**SAEs:** In study 003, a combined number of 3/74 (4.1%) patients who received 75 mg AI BID (1 patient) and 225 mg BID (2 patients) reported at least one SAE compared to 2/31 (6.5%) patients who reported at least one SAE in the placebo-treated arm. The number of patients reporting

SAEs in study 003 was small and the incidence of SAE reports was comparable in the study arms.

In study 005, a combined number of 15/135 (11.1%) who received AI 75 mg BID (7 patients) and 75 mg TID (8 patients) reported at least one SAE compared to 4/76 (5.3%) in the pooloed placebo arn who reported at least one SAE. Thus, the rate of SAE reports in the AI-treated patients was slightly more than double that in the placebo-treated patients.

In study 007, 5/80 (6.3%) AI-treated patients reported at least one SAE compared to 12/84 (14.3%) placebo-treated patients.

**Treatment-related SAE (TRSAE):** Only 1/84 (1.2%) patient in the placebo arm reported at least one TRSAE in this group (double-blind) of studies.

**Other AEs:** The rates of reporting at least one AE by patients in study 003 who received the two different doses of AI (75 mg vs 225 mg) were similar (73.0% vs 78.4% respectively). But, combining the two AI arms in comparison with the placebo arm, 56/74 (75.7%) patients who received AI reported at least one AE. This was similar to 24/31 (77.4%) in the palacebo arm.

In study 005, 66/69 (95.7%) patients who received AI BID and 62/66 (93.9%) patients who received AI TID reported at least one AE; these rates were similar to the rate in the placebo arm where 70/76 (92.1%) patients reported at least one AE. Pooling the AI arms, 128/135 (94.8%) reported at least one AE at a rate similar to that of the placebo arm where 92.1% reported at least one AE.

In study 007, 66/80 (82.5%) patients who received AI TID and 68/84 (81%) patients who received placebo TID reported at least one AE; these rates were similar.

**Treatment-related AE (TRAE):** In the combined two AI arms of study 003, 23/74 (31.1%) patients reported at least one TRAE compared to 7/31 (22.6%) patients in the placebo arm of the same study. Thus, a higher rate of reporting (31.1%) occurred in the AI-treated patients than in placebo-treated patients (22.6%).

In study 005, 21/69 (30.4%) who received AI BID and 23/66 (34.8%) who received AI TID, [or 44/135 (32.6%) in the combined AI groups], reported at least one TRAE compared to 24/76 (31.6%) patients who received placebo. The rates were similar across study arms.

In study 007, 31/80 (38.8%) patients who received AI TID and 19/84 (22.6%) patients who received placebo TID reported at least one TRAE. Patients who received AI TID reported a higher rate of TRAE than placebo-treated patients.

**Adverse Events Leading to Patient Discontinuation**
Patient discontinuations resulting from AEs during trials of AI are summarized for the individual phase 2/3 studies of AI in table S4a. Most study discontinuations due to AEs were associated

with signs and symptoms of pulmonary exacerbations, and most of the associated AEs were considered by the investigator to be unrelated to the study drug.

In both AI arms of study 003, 5/74 (6.8%) versus 2/31 (6.5%) placebo patients were discontinued from study. Of these, 1/74 (1.4%) AI-treated patient versus 1/31 (3.2%) who received placebo experienced discontinuation from study due to TRAE.

Also in both AI arms of study 005, 71/135 (52.6%) versus 50/76 (65.8%) patients who received placebo were discontinued from study. Of these, 15/135 (11.1%) AI-treated patients versus 23/76 (30.3%) patients who received placebo were discontinued from study due to TRAE.

According to the Sponsor, in study 007, 13/80 (16.3%) AI-treated patients versus 27/84 (32.1%) placebo-treated patients were discontinued from the study. Of these, 3/80 (3.8%) AI-treated patients compared to 5/84 (6.0%) who received placebo were discontinued from the study due to TRAE.

**An Overview of AEs in the Open-Label Study 006**

The two study arms in study 006 were 75 mg AI BID and 75 mg AI TID. Patients were enrolled from study 005 into this study to continue with regimen received in study 005. There was no placebo arm in this study.

**Death:** One death occurred in study 006 (see section 7.3.1).

**SAEs and TRAEs:** Among the patients in AI BID arm, 34/82 (41.5%) reported at least one SAE; in the AI TID arm, 47/125 (37.6%) reported at least one SAE. Of these, 4/82 (4.9%) patients in the BID arm vs 6/125 (4.8%) patients in the AI TID arm reported at least one TRSAE. The rates were comparable.

**Other AEs:** In the BID arm, 45/82 (54.9%) reported at least one AE compared to 68/125 (54.4%) patients in the TID arm. In the former, 25/82 (30.5%) reported at least one TRAE compared to latter subgroup where 48/125 (38.4%) patients reported at least one TRAE. The rates of patients reporting at least one AE or TRAE were comparable across the two different regimen (BID vs TID) arms.

## Table S4a: Overview of Adverse Events in Study Patients

| Table 7S3: | Double-Blind Studies 003, 005, and 007 Patients | | | | | | | | Open label study Patients | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Study 003 | | | Study 005 | | | Study 007 | | Study 006 | |
| Number (%) of patients reporting: | 75 mg BID | 225 mg BID | Placebo | 75 mg BID | 75 mg TID | Pooled Placebo | 75 mg TID | Placebo | 75 mg BID | 75 mg TID |
| | N = 37 | N = 37 | N = 31 | N = 69 | N = 66 | N = 76 | N = 80 | N = 84 | N = 82 | N = 125 |
| at least one AE | 27 (73.0) | 29 (78.4) | 24 (77.4) | 66 (95.7) | 62 (93.9) | 70 (92.1) | 66 (82.5) | 68 (81) | 45 (54.9) | 68 (54.4) |
| at least one treatment-related AE | 10 (27.0) | 14 (37.8) | 6 (19.4) | 21 (30.4) | 23 (34.8) | 24 (31.6) | 31 (38.8) | 19 (22.6) | 25 (30.5) | 48 (38.4) |
| | | | | | | | | | | |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Death from Study-drug related AE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | | | | |
| at least one SAE | 1 (2.7) | 2 (5.4) | 2 (6.5) | 7 (10.1) | 8 (12.1) | 4 (5.3) | 5 (6.3) | 12 (14.3) | 34 (41.5) | 47 (37.6). |
| at least one treatment-related SAE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.2) | 4 (4.9) | 6 (4.8) |
| | | | | | | | | | | |
| AE→ withdrawal from study | 3 (8.1) | 2 (5.4) | 2 (6.5) | 32 (46.4) | 39 (59.1) | 50 (65.8) | 13 (16.3) | 27 (32.1) | 16 (19.5) | 30 (24) |
| Drug-related AE→ withdrawal | 1 (2.7) | 0 | 1 (3.2) | 6 (8.7) | 9 (13.6) | 23 (30.3) | 3 (3.8) | 5 (6.0) | 3 (3.7) | 8 (6.4) |
| | | | | | | | | | | |
| AE → study drug discontinuation | 1 (2.7) | 1 (2.7) | 1 (3.2) | | | | | | | |
| | | | | | | | | | | |
| Total Number of AEs | 53 | 62 | 66 | 115 | 110 | 140 | 315 | 348 | 872 | 1344 |
| | | | | | | | | | | |
| → = Leading to or causing | | | | | | | | | | |

***MO comments:*** *Differences in reporting rates of at least one AE/SAE among patients were sought between 1) AI-treated and placebo-treated patients; 2) patients who received different doses of AI (e.g. AI 225 mg vs AI 75 mg in two of the three arms of study 003); 3) across different regimens (e.g. BID vs TID, as in study 005); and 4) across studies that used different durations of AI (e.g., 14 days of AI, as in study 003, vs 28 days of AI, as in studies 005 and 007). Despite these differences across studies and study arms, the overall reporting rates of at least one AE/SAE across these divides were mostly comparable. Exceptions included: a) the rate of reporting at least one TRAE in the 225 mg AI arm of study 003 was 14/37 (37.8%); it was either comparable to or just slightly higher than the lower dose (75 mg BID) arm [10/37 (27.0%)]. It was much higher than the rate in the placebo arm [6/31 (19.4%)]. Similarly, in study 007, 31/80 (38.8%) patients who received AI reported at least one TRAE compared to 19/84 (22.9%) who received placebo. Conversely, in study 007, 13/80 (16.3%) AI-treated patients versus 27/84 (32.1%) placebo-treated patients were discontinued from the study. There were therefore more AEs in the placebo arm leading to patient discontinuations from the study than AI-treated patients.Some of the denominator numbers, however, were relatively small.*

*The total numberof reported AEs seemed to have a linear relationship with the number of patients enrolled or treated in individual studies.*

### *7.3.1 Deaths*

There was one death in the AI clinical development program. A narrative of events preceding her death follows.

**Narrative**

Patient 15206 was enrolled from study 005 and became patient #152602 in study 006. She was a Caucasian female with CF who was 44 years old at the time of her death during her fourth hospitalization. She died from hemoptysis after one course of AI BID in study 005, followed by seven courses of AI 75 mg BID in study 006. Her death was considered unlikely to be related to the study drug by the investigator.

Her medical history included intermittent hemoptysis; embolization procedures; chronic bronchitis and sinusitis; asthma; seasonal and drug allergies; CF-related malabsorption, pancreatic insufficiency, and diabetes; and multiple exacerbations of CF lung disease.
At Day 0 in Study 005, the patient's $FEV_1$ % predicted was 36%. Although she completed her 28-day course of AI in study-005, she was discontinued from the study on Day 56 due to mild hemoptysis. She completed an Early Termination Visit and was altogether withdrawn from the study. Forty two days after discontinuation from study-005, she was enrolled into study 006 and began the second course of AI (75 mg BID). Altogether, she spent 17 months in study 006 where she received seven courses of AI (eight courses altogether).

**First hospitalization -** occurred during the third cycle of AI and was admitted for "worsening of hemoptysis" which was considered severe. She then underwent a planned embolization of the right bronchial artery and two branches of the left bronchial artery. The hemoptysis resolved three weeks later.

**Second hospitalization -** occurred after completing four courses of AI and was admitted for "massive hemoptysis and respiratory distress". She was intubated for 24 hours for the massive hemoptysis. She also had non-cardiac chest pain; considered a CF-related lung disease exacerbation. An admission chest X-ray showed stable chronic changes with suspected mucoid impaction at the bases, with a possible right lower lobe pneumonia. She underwent two embolization procedures after which she experienced no further episodes of hemoptysis.

**Third hospitalization -** occurred after completing the fifth course of AI and was admitted for "hemoptysis" of severe intensity. This episode resolved without embolization.

**Fouth hospitalization-** occurred after completing the eighth course of AI and was admitted for "worsening of hemoptysis". Similar to the third hospitalization, the hemoptysis resolved.

**Patient Death** - the data cut off occurred on March 01, 2007, about two weeks after patient had completed eight courses of AI. The patient died on (b) (6), about a month after the last dose of AI. She suffered massive hemoptysis and, consequently, cardiac arrest – and death.

Per the Sponsor, all events of hemoptysis, and all other AEs experienced by the patient during the periods of hospitalization, were considered unlikely to be related to the study drug by the investigator.

**Possible Emergence of Resistant *P. aeruginosa* in this Patient after Eight AI Cycles**

According to the Sponsor, analysis of MIC data for this patient indicated no emergence of resistant *P. aeruginosa* due to AI treatment. Coming into study 006, no baseline bacteriologic data from study 005 were available for this patient. Her lowest aztreonam MIC (16 µg/mL) was recorded two weeks after beginning the first AI treatment in study 005 and the highest MIC (256 µg/mL) was recorded two weeks after her last dose. Four weeks after the last dose in study 005, the MIC was 64 µg/mL.

The Sponsor reported that multi-drug resistant *P. aeruginosa* was cultured from the patient at baseline of the open-label study (study 006), but no treatment-related resistance to aztreonam was observed. In study 006, the highest aztreonam MIC values recorded were 128 µg/mL at the earliest visit and 256 µg/mL at the latest visit; transient increases to 512 µg/mL were observed at the end of treatment courses one and four.

***MO Comments:*** *Attribution of this patient's death to the receipt of AI is a difficult argument to make. The 43 year-old female was initially enrolled into study 005 (AI BID arm) and was 44 at the time of her death at which time, she had received eight courses of AI (one course in study 005, seven courses in study 006). At the time of enrollment, her $FEV_1$ was ≤50 % predicted. In study 005, patients with $FEV_1 \leq 50\%$ predicted fared worse than their counterparts in the less severe disease category, as they required inhaled or IV antibiotics due to warning signs and symptoms of exacerbaton at a higher rate than patients with less severe disease (> 50% $FEV_1$ predicted).*
*During the study period, patients had received at least seventy nine other medications for the management of her CF, including nine different antibiotic products (azithromycin, ciprofloxacin, cefepime, meropenem, ceftazidime, levofloxacin, minocycline, ticarcillin, tobramycin and inhalational TOBI). She had been hospitalized four times with episodes of hemoptysis.To be sure, hemoptysis is not an uncommon AE in CF patients, partly in association with disease progression or deterioration. For example, in study 005 into which this patient was initally enrolled, 8/69 (11.6%) patients, including the patient, reported hemoptysis as an AE compared to 6/38 (15.8%) in the placebo BID arm. In patients who received the TID regimen in the combined study 005 and 007 16/146 (11.0%) AI TID-treated patients compared to 14/122 (11.5%) placebo-treated patients reported hemoptysis as an AE. In study 006, 27/125 (21.6%) who received 75 mg AI TID versus 20/82 (24.4%) who received 75 mg AI BID reported hemoptysis as an AE. This lady's case seemed relatively more severe and recurrent. For instance, it was described as "worsening" on the first hospitalization and "massive on the second and last (fourth) hospitalizations. She had also been infirmed by her worsening CF disease and probably further compromised by the need for arterial embolization that complicated her condition. Thus, due to her numerous (tangible and intangible) confounding factors, a causality attribution of this patient's demise to the receipt of AI could not be firmly established.*

### *7.3.2 Nonfatal Serious Adverse Events*

Table S4a and S4b display the SAEs reported by study patients who participated in the double-blind placebo-controlled studies 007 and 005 following the receipt of AI or placebo. The numbers (and percentages) of the study patients reporting SAEs are also shown according to the SAEs reported and the regimens received. Tables S5 and S6 show data analyses from patients in study 003 and study 006 respectively.

## Reviewer's Method of SAE and other Safety Data Review

In table S4a, SAE data derived from study 005 were divided into two separate parts in accordance with the regimen received (BID or TID). Patients who received BID regimen (AI versus placebo) were compared and analyzed (AI BID arm against placebo BID arm). The patients who received BID regimen (AI versus placebo) were analyzed separately on the right part of the table. This was to ascertain possible regimen-related SAE frequency among patients who received the BID regimen. Data from study 005 patients who received TID regimen (AI or placebo) and who reported SAEs as well as all study 007 patients who reported SAEs (as all patients in this study received TID regimen), were pooled and analyzed first on the left part of the table for comparison (AI TID arm vs placebo TID) given that this is the regimen proposed for marketing by the Sponsor.

SAE data from study 003 were analyzed separately in table S5 for comparison of dose/duration-related reported SAE frequency. SAE frequency data from the open-label study 006 patients were analyzed in table S6.

**SAEs in Studies 005 and 007**

The SAEs most frequently reported by study patients (≥ 2% in any arm) are listed in the upper tier of table S4a. For patients who received BID regimen, 69 patients received AI vs 38 patients who received placebo. As expected, where the denominator was small, e.g., the BID placebo arm of study 005, AE/SAE rates appeared large relative to another study arm with a larger denominator. The largest arm in table S4a/S4b and subsequent corresponding tables for studies 005 and 007 analyzed, was AI TID arm (N= 146).

Among the patients who received AI or placebo treatment (TID or BID), cough (productive and non-productive) were the most common SAEs and occurred at higher rates in placebo arm than in the AI arm. As table S4a indicates, 4/146 (2.7%) AI-treated patients reported pneumonia compared to none in placebo-treated patients. This was the notable difference between both arms. Decreased pulmonary function testing occurred in 4/146 (2.7%) in AI-treated patients compared to 2/122 (1.6%) placebo-treated patients. These were fairly comparable. The rest of the most common SAEs and other SAEs in tables S4a and S4b were either similar across study arms or were reported at higher rates in the placebo arm than in the AI arm.

Patients who received placebo BID reported the least number of SAEs. Only two patients reported SAEs in that arm of study: 1/38 (2.6%) reported productive cough compared to 3/69 (4.3%) patients who received AI BID. The other patient in the placebo BID arm who reported SAE reported tachycardia. No patients in the AI BID arm reported tachycardia. Among the other SAEs reported by patients who received AI BID treatment, 2/69 (2.9%) patients reported cough. The same number reported respiratory tract congestion compared to none in the placebo BID arm. Each of the other SAEs in the AI BID arm was reported by one patient each, as shown in tables S4a and S4b. The SAEs were charaterized as moderate to severe. None was considered study drug-related. All but one recovered completely. Patient 40108 had spinal cord injury and recovered with sequelae.

**Number (%) of SAEs Reported by Phase 3 (Double-Blind) Study Patients**

| **Table S4a:** | **Number (%) of SAEs Reported by Phase 3 (Double-Blind) Study Patients** | | | |
|---|---|---|---|---|
| **SAEs (Preferred term)** | **Phase 3 Double –Blind Studies** | | | |
| ⇓ | **Pooled Study 007 & Study 005 (TID Arms Only)** | | **Study 005 (BID Arms Only)** | |
| | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| **Most common SAEs** | N = 146 | N = 122 | N = 69 | N = 38 |
| Cough (Productive) | 4 (2.7) | 6 (4.9) | 3 (4.3) | 1 (2.6) |
| Cough | 5 (3.4) | 5 (4.1) | 2 (2.9) | - |
| Pneumonia | 4 (2.7) | - | - | - |
| Pulmonary function test decreased | 4 (2.7) | 2 (1.6) | 1 (1.5) | - |
| Dyspnoea (& exacerbated dyspnoea) | 4 (2.7) | 7 (5.7) | - | - |
| Fatigue | - | 3 (2.5) | - | - |
| Respiratory tract congestion | 1 (0.7) | 1 (0.8) | 2 (2.9) | - |
| Tachycardia | - | - | - | 1 (2.6) |
| **Other SAEs** | | | | |
| Abdominal pain | 1 (0.7) | - | 1 (1.5) | - |
| Arthralgia | - | - | - | - |
| Asthenia | - | 1 (0.8) | - | - |
| Blood glucose increased | 1 (0.7) | - | - | - |
| Breath sounds decreased | 1 (0.7) | - | - | - |
| Chest discomfort | 1 (0.7) | - | - | - |
| Chest X-ray abnormal | - | - | 1 (1.5) | - |
| Crackles (Lung) | 1 (0.7) | 2 (1.6) | 1 (1.5) | - |
| CRP increased | 1 (0.7) | - | - | - |
| Decreased appetite | 1 (0.7) | - | - | - |
| Dehydration | - | 1 (0.8) | - | - |
| CRP = C-reactive protein | | | | |

***MO comments:*** *Overall, 17/69 (24.6%) patients who received AI BID reported SAEs compared to 2/38 (5.3%), 46/146 (31.5%) or 6/122 (37.7%) patients who received placebo BID, AI TID or placebo TID respectively. Thus, patients who received placebo TID reported the highest rate of*

*SAEs. Conversely, patients who received placebo BID reported the lowest rate of SAEs, although, this assessment should be taken in the context of a low denominator (N=38). In terms of individual SAE, although cough (productive and otherwise) were the most reported SAEs, in the TID arms, they were reported at slightly higher rates in the placebo arm than in the AI arm. Pneumonia was the one SAE reported only in the AI TID arm alone.*

| **Table S4b:** | **Number (%) of SAEs Reported by Studies 007 and 005 Patients** | | | |
|---|---|---|---|---|
| **SAEs (Preferred term)** | **Phase 3 Double –Blind Studies** | | | |
| ⇓ | **Pooled Study 007 & Study 005 (TID Arms Only)** | | **Study 005 (BID Arms Only)** | |
| | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| **Other SAEs (continued)** | N = 146 | N = 122 | N = 69 | N = 38 |
| Erythema | 1 (0.7) | - | - | - |
| Exercise tolerance decreased | - | 2 (1.6) | - | - |
| $FEV_1$ decreased | - | - | 1 (1.5) | - |
| Haemoptysis | 1 (0.7) | 1 (0.8) | - | - |
| Hypoxia | 1 (0.7) | 1 (0.8) | - | - |
| Hypovolaemia | - | 1 (0.8) | - | - |
| Injury | - | - | - | - |
| Intercostal retraction | - | 1 (0.8) | - | - |
| Intestinal obstruction | 1 (0.7) | 1 (0.8) | 1 (1.5) | - |
| Lobar pneumonia | - | - | - | - |
| Lung disorder | - | - | - | - |
| Malnutrition | - | 1 (0.8) | - | - |
| Musculoskeletal chest pain | 1 (0.7) | - | - | - |
| Nausea | 1 (0.7) | - | - | - |
| Neck pain | - | - | 1 (1.5) | - |
| Neurological symptom | 1 (0.7) | - | - | - |
| Non-cardiac chest pain | 2 (1.4) | 1 (0.8) | - | - |
| Oedema peripheral | 1 (0.7) | - | - | - |
| Oxygen saturation decreased | - | 2 (1.6) | - | - |
| Pain (NOS) | - | - | - | - |
| Pain in extremity | 1 (0.7) | 1 (0.8) | - | - |
| Pleural effusion | 1 (0.7) | - | - | - |
| Perirectal abscess | - | - | 1 (1.5) | - |
| Pyrexia | 2 (1.4) | 1 (0.8) | 1 (1.5) | - |
| Sinus congestion | - | 1 (0.8) | - | - |
| Spinal cord injury | - | - | 1 (1.5) | - |
| Sputum discoloured | - | 2 (1.6) | - | - |
| Tachypnoea | 1 (0.7) | - | - | - |
| Thrombosis | - | 1 (0.8) | - | - |
| Umbilical hernia | - | 1 (0.8) | - | - |
| Wheezing | 2 (1.4) | - | - | - |
| → = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified | | | | |

**Treatment-Related SAEs in Studies 007 and 005**
Only one patient (027459 - in study 007) reported an SAE of hemoptysis that was considered treatment-related. The patient received placebo treatment.

**SAEs in Study 003 Patients**
Only five patients reported SAEs in study 003 – 2/37 (5.4%), 1/37(2.7%) and 2/31 (6.5%) reported these SAEs in the 225 mg, 75 mg and placebo BID arms respectively. The number of patients reporting these SAEs and the types of SAEs reported are shown in table S5.

**Number (%) of Patients Reporting SAEs in Study 003**

| **Table S5** | **Number (%) of Patients Reporting SAEs in Study 003** | | |
|---|---|---|---|
| | **Study 003** | | |
| **SAEs (Preferred term)** | 225 mg BID | 75 mg BID | Placebo BID |
| | N = 37 | N = 37 | N = 31 |
| Arthralgia | 1 (2.7) | - | - |
| Injury | 1 (2.7) | - | - |
| Lobar pneumonia | - | - | 1 (3.2) |
| Lung disorder | - | 1 (2.7) | 1 (3.2) |
| | | | |

***MO comments:*** *The number of patients reporting SAEs in study 003 is small. Given this small number, no trends were expected. No dose-related SAE incidence was discernable.*

**Treatment-Related SAEs in Study 003**
There were no treatment-related SAEs in study 003.

**Study 006**
The primary objective of this open-label follow-on study was to evaluate the safety of repeated exposure to AI in CF patients. Patients enrolled in this study were required to have previously participated in study 005 or study 007. Patients from study 005 received the same regimen (75 mg BID or 75 mg TID) that they were previously randomized to receive. Patients in study 007 received 75 mg TID regimen used in the study. One hundred and fifty-six patients were enrolled from study 005 and 51 patients were enrolled from study 007. The total time a patient could be in the study was about 18 months, or until the product (AI) became commercially available, whichever occurred sooner. At the time this part of the review was being done (June 2008), study 006 was still on-going.

***SAEs Reported in Study 006***

Table S6a and S6b show the SAEs reported in the open-label study 006. A larger number of study patients seemed to have reported SAEs in this study than the blinded studies 007, 005 and 003. The most common SAEs (reported by ≥ 3% of study population) are listed on the upper tier of table S6a. Cough and productive cough were the most frequently reported SAEs and were reported at rates that were similar in TID-treated and BID-treated patients. Cough was reported by 27/125 (21.6%) patients who received 75 mg TID compared to 17/82 (20.7%) patients who

received 75 mg BID treatment. In addition, 14/125 (11.2%) patients who were receiving 75 mg TID reported productive cough as an SAE compared to 11/82 (13.4%) in patients receiving 75 mg BID treatment.
The SAE of "pulmonary function test decreased" (by preferred term) was reported at a much higher rate in the TID arm than in the BID arm of the study. This was reported in 15/125 (12.0%) patients who received TID regimen compared to 1/82 (1.2%) who received BID regimen. Dyspnea, hemoptysis, fatigue and abdominal pain were other SAEs reported at slightly higher rates than the corresponding rates in the BID arm. The other SAE rates were lower and generally comparable across study arms. These less frequently reported SAEs are listed in tables S6a and S6b in alphabetical order.

***SAEs in open-label Study 006***

| **Table S6a** | **Number (%) reporting SAEs in study 006** | |
|---|---|---|
| **Reported SAEs (Preferred Term)** | **AI 75 mg TID (N = 125)** | **AI 75 mg BID (N = 82)** |
| **Most Common SAEs** | | |
| Cough | 27 (21.6) | 17 (20.7) |
| Productive cough | 14 (11.2) | 11 (13.4) |
| Dyspnoea (including exacerbated /exertional dyspnoea) * | 16 (12.8) | 7 (8.5) |
| Pulmonary function test decreased | 15 (12.0) | 1 (1.2) |
| Haemoptysis | 6 (4.8) | 3 (3.7) |
| Fatigue | 6 (4.8) | 2 (2.4) |
| Abdominal pain (including upper and lower) | 6 (4.8) | 2 (2.4) |
| Pyrexia | 5 (4.0) | 4 (4.9) |
| Respiratory tract congestion | 5 (4.0) | 2 (2.4) |
| Rhinorrhoea | 4 (3.2) | - |
| Exercise tolerance decreased | 4 (3.2) | 3 (3.7) |
| **Other SAEs** | | |
| Antibacterial prophylaxis | 2 (1.6) | 2 (2.4) |
| Arthralgia | - | 1 (1.2) |
| Asthenia | - | 1 (1.2) |
| Back pain | - | 1 (1.2) |
| Blood culture positive | 1 (0.8) | - |
| Blood chloride decreased | 1 (0.8) | - |
| Blood creatinine increased | 1 (0.8) | - |
| Breath sounds decreased | 1 (0.8) | - |
| Bronchiectasis | 1 (0.8) | - |
| Chest discomfort | 1 (0.8) | 3 (3.7) |
| Constipation (§) | 2 (1.6) | - |
| Crackles (lung) | 3 (2.4) | 1 (1.2) |
| Decreased appetite | 3 (2.4) | 1 (1.2) |
| Dehydration | 1 (0.8) | - |
| Diarrhoea | 1 (0.8) | - |
| Dizziness | 1 (0.8) | - |
| Electrolyte imbalance | 1 (0.8) | - |
| $FEV_1$ decreased | 2 (1.6) | 1 (1.2) |

## SAEs in Study 006 (continued)

| Table S6b | Number (%) reporting SAEs in study 006 | |
|---|---|---|
| **Reported SAEs (Preferred Term)** | **AI 75 mg TID (N = 125)** | **AI 75 mg BID (N = 82)** |
| **Other SAEs (continued)** | | |
| Gastrostomy tube insertion | - | 1 (1.2) |
| Gastrointestinal disorder | 1 (0.8) | - |
| Headache | 3 (2.4) | - |
| Hepatitis acute | 1 (0.8) | - |
| Hyperglycaemia | 1 (0.8) | - |
| Hypoxia | 2 (1.6) | 1 (1.2) |
| Infrequent bowel movements (§) | - | 1 (1.2) |
| Inguinal hernia | 1 (0.8) | - |
| Joint swelling | 1 (0.8) | 1 (1.2) |
| Lipase increased | 1 (0.8) | - |
| Lung disorder | 1 (0.8) | - |
| Lung infiltration | - | 1 (1.2) |
| Nausea | 2 (1.6) | - |
| Nephrolithiasis | - | 1 (1.2) |
| Non-cardiac chest pain | 1 (0.8) | 1 (1.2) |
| Oxygen consumption increased | 1 (0.8) | 1 (1.2) |
| Oxygen saturation decreased | 1 (0.8) | 3 (3.7) |
| Pancreatitis | 1 (0.8) | 1 (1.2) |
| Pharyngolaryngeal pain | 1 (0.8) | 1 (1.2) |
| Pneumonia | 1 (0.8) | 1 (1.2) |
| Pneumothorax | - | 1 (1.2) |
| Pulmonary function test decreased | - | 1 (1.2) |
| Rash | 1 (0.8) | - |
| Respiratory distress * | - | 1 (1.2) |
| Rhonchi | - | 1 (1.2) |
| Sinus operation | - | 1 (1.2) |
| Sinus congestion | 1 (0.8) | - |
| Sputum discoloured | 2 (1.6) | 2 (2.4) |
| Uterine leiomyoma | 1 (0.8) | - |
| Vomiting | 2 (1.6) | 1 (1.2) |
| Weight decreased | 1 (0.8) | - |
| Wheezing | - | 1 (1.2) |

***MO comments:*** *Although study 006 was an open-label study, it has demonstrated that the most frequently reported SAEs in the study were cough and productive cough, consistent with the double-blind Phase 3 studies. Dyspnea and decreased pulmonary function testing also ranked high in frequencies of SAE occurrences, although all were reported at much higher frequencies in study 006 than in the double-blind studies 007, 005 and 003. This is in all likelihood related to patients in this study having received more drug exposure through multiple cycles and for extended periods of time in this open label study. Although the SAE rates for BID and TID treatment arms are shown side-by-side for study 006, comparisons should be made with caution.*

*These were not randomized treatment groups; they are patients who elected to continue in the open-label treatment with AI TID or AI BID after participation in the randomized studies.*

Table S7 displays SAEs determined by investigators to be study-drug related. As shown in the table, they were relatively few in number and no appearance of regimen-related frequency of the SAEs is apparent.

**Treatment-Related SAEs in Study 006**

| **Table S7** | | |
|---|---|---|
| **Treatment-Related SAEs** | **AI 75 mg TID (n = 125)** | **AI 75 mg BID (n = 82)** |
| Arthralgia | - | 1 (1.2) |
| Breath sounds decreased | 1 (0.8) | - |
| Cough | 1 (0.8) | 1 (1.2) |
| Dyspnoea exacerbated | 1 (0.8) | |
| Joint swelling | - | 1 (1.2) |
| Productive cough | 1 (0.8) | 1 (1.2) |
| Pulmonary function test decreased | 1 (0.8) | - |
| Rash | 1 (0.8) | - |

***MO comments:*** *Treatment-related SAEs (TRSAEs) in the open-label study (006) were few. All the TRSAEs as displayed in table S7 were actually reported by only four patients, two in each arm of the study. Three of them were hospitalized.*

***Patient 063415*** *was a 24 year-old a white female (WF) whose lung severity status was categorized as $FEV_1 \leq 50\%$ predicted. She was in the 75 mg AI TID arm of study 006. She had CF-related diabetes mellitus. In addition to her SAEs, she had reported multiple AEs, including hemoptysis, decreased weight and decreased exercise tolerance. She reported the SAEs of increased cough, productive cough, exacerbated dyspnoea; her evaluation revealed decreased breath sounds and decreased pulmonary function test (PFT) by >15%. The cause of the decrease, e.g. whether it was related to bronchospasm versus worsening lung status, was not further described. She was initially hospitalized from* (b) (6) *for pulmoary exacerbation and subsequently from* (b) (6) *Symptoms resolved.*

***Patient 002181*** *was a 38 year WF who was in the 75 mg AI TID arm of in study 006. Her $FEV_1$ was > 50% predicted at baseline. She developed chest discomfort, throat tightness and mild to moderate hemoptysis. She was hospitalized for 12 days for the management of her hemoptysis. Her sputum culture was found positive for Mycobacterium abscessus and her blood culture was positive for yeast. She developed diffuse rash and swollen lips which all resolved within two days. Given the severity (being diffuse) and rather transient nature of her rash, it could have been an allergic type rash although the Sponsor gave no specific name to the rash.*

***Patient 005316*** *was a 15 year old WF at the time of her reporting SAE. She had $FEV_1$> 50% predicted in her pulmonary function test at baseline. She was receiving 75 mg AI BID. She reported increased cough, productive cough, decreased exercise tolerance, fatigue and dyspnea. She was hospitalized for pulmonary exacerbation symptoms. Patient had multiple extended admissions. All symptoms resolved and patient apparently continued in the study although it was not explicitly stated.*

***Patient 005190*** *was a 19 year-old WF during the study. Her $FEV_1$ was ≤ 50% predicted and was in the 75 mg AI BID arm of study 006. She reported many AEs, including tachycardia, pruritus and rash; cough and productive cough; and peripheral edema. She subsequently reported multiple joint pain involving her wrists, elbows as well as shoulder and ankles.She also reported swelling of wrists and hands. The symptoms resolved in 11 to 12 days. She was not hospitalized.*

***SAEs in Phase 1 studies 001 and 002***

No serious adverse events were recorded in Phase 1 studies.

***7.3.3 Dropouts and/or Discontinuations***

Tables S8 through S10 enumerate the numbers and rates of dropouts or discontinuations from studies 007 and 005 (table S8), study 003 (table S9) and study 006 (table S10). In some patients, study drugs were discontinued. These were the patients in the "Study drug Rx intolerance & documented AE" category in the tables of discontinuations (S8 through S10). Other patients were discontinued or withdrawn from their studies altogether.

The reasons for dropping out (or being discontinued) from applicable study (or studies) are listed in the individual tables. There was a subset of patients in each study in which the reason for discontinuation from study was listed as "other". The various reasons given by patients that were lumped together under the rubric of "other" are listed in table S11. The category of patients that dropped out due to study drug-related AEs was of particular interest to this review because of potential association with the receipt of AI.

As shown in table S8, the overall rate of discontinuation from study was higher in the placebo arm than in AI arm of the studies (BID or TID). For patients in studies 005 and 007, the most common AEs leading to discontinuation from study were AEs unrelated to study drugs or study procedures.They were slightly higher in frequencies in the placebo arms than in the AI arms (whether BID or TID). Per the dataset provided, drug-related or study procedure-related AEs also occurred at higher rates in the placebo arms than in the AI arms (whether BID or TID). However, 4/69 (5.8%) study patients in the AI BID arm were discontinued from the study for "other" reasons compared to 1/38 (2.6%) in the placebo BID arm. The rate of discontinution for "other" in the AI BID-treated patients was more than twice higher (5.8%) than in the placebo BID arm (2.6%). The figures (and rates) involved were small.

## Dropouts/Discontinuations: Studies 005 and 007 Patients

| Table S8 | Number (%) of Dropouts /Discontinuations in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Pooled Studies 007 & 005 (TID arms Only) | | Study 005 (BID Arms Only) | |
| Reason for Dropout/Discontinuation | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ Due to AEs | N = 146 | N = 122 | N = 69 | N = 38 |
| Overall | 52 (35.6) | 57 (46.7) | 32 (46.4) | 20 (52.6) |
| AE Related to study drug/study procedures | 12 (8.2) | 14 (11.5) | 6 (8.7) | 4 (10.5) |
| AE Unrelated to study drug/study procedures | 34 (23.3) | 36 (29.5) | 21 (30.4) | 14 (36.8) |
| Non-compliance | 1 (0.7) | - | 1 (1.5) | - |
| Other | 1 (0.7) | 3 (2.5) | 4 (5.8) | 1 (2.6) |
| Personal or administrative reasons | 2 (1.4) | 1 (0.8)_ | - | 1 (2.6) |
| Study drug Rx intolerance & documented AE | 1 (0.7) | 2 (1.6) | - | - |
| Lost to follow-up | 1 (0.7) | 1 (0.8)_ | - | - |

***MO's Comments:*** *Table S8 shows the dropout profiles of patients in studies 005 and 007 as reproduced from the datasets from the Sponsor. There were higher rates of discontinuations in the placebo-treated patients in nearly all categories listed than in AI-treated patients, even among the patients who reported drug-related AEs. The exception (where more than 2 patients were involved) was in the "other" category where 4/69 (5.8%) in the AI BID arm were discontinued compared to 1/38 (2.6%) in the placebo BID arm. The reasons under the rubric of "other" are presented in table S11.*

### Dropouts and/or Discontinuations in Studies 003

The number of patients and rates of dropouts/discontinuations in the three arms of study 003 are as displayed in table S9. The numbers across study arms are few and are comparable in the "AE unrelated to study drug/study procedures" category. Only one patient in the placebo arm had an AE that was considered drug-related. In addition, one patient in the 75 mg BID study arm had intolerance to study drug which was discontinued and was documented as an AE.

**Dropouts /Discontinuations: Study 003**

| **Table S9:** | **Number (%) of Dropouts /Discontinuations in Study 003** | | |
|---|---|---|---|
| **Reason for Dropout/Discontinuation** | **225 mg BID** | **75 mg BID** | **Placebo BID** |
| ⇓ **Due to AEs** | **N = 37** | **N = 37** | **N = 31** |
| AE Related to study drug/study procedures | - | - | 1 (3.2) |
| AE Unrelated to study drug/study procedures | 2 (5.4) | 2 (5.4) | 1 (3.2) |
| Non-compliance | - | - | - |
| Other | - | - | - |
| Personal or administrative reasons | - | - | - |
| Study drug Rx intolerance & documented AE | - | 1 (2.7) | - |
| Lost to follow-up | - | - | - |

***MO's Comments:*** *Table S9 shows the dropout profiles of patients in studies 003 as reproduced from the datasets from the Sponsor. The patients involved in these discontinuations are as shown in the table. The one patient whose discontinuation was due to study therapy was in the placebo arm of the study.*

**Dropouts and/or Discontinuations in Studies 006**

The number and rates of discontinuations in study 006 are as shown in table S10. There was one patient who died. This case was already discussed in datail in section 7.3.1. Aside from the "other" category where 4/82 (4.9%) of patients who received 75 mg BID were discontinued compared to 2/125 (1.6%) in the 75 mg TID arm who were discontinued for similar reasons, the rates of dicontinuations in in the other categories were either comparable across study arms or they were slightly higher in the 75 mg TID arm. The reasons described as "other" as they pertain to study 006 patients are listed in table S11.

**Dropouts /Discontinuations: Study 006**

| **Table S10** | **Number (%) of Dropouts /Discontinuations Among Study 006 Patients** | |
|---|---|---|
| **Reason for Dropout/Discontinuation** | **75 mg TID** | **75 mg BID** |
| ⇓ **Due to AEs** | **N =125** | **N = 82** |
| Death | - | 1 (1.2) |
| AE Related to study drug/study procedures | 2 (1.6) | 1 (1.2) |
| AE Unrelated to study drug/study procedures | 5 (4.0) | 2 (2.4) |
| Non-compliance | 3 (2.4) | - |
| Other | 2 (1.6) | 4 (4.9) |
| Personal or administrative reasons | 10 (8.0) | 5 (6.1) |
| Study drug Rx intolerance & documented AE | 5 (4.0) | 2 (2.4) |
| Lost to follow-up | 3 (2.4) | 1 (1.2) |

**Reasons for Discontinuation from Study: Content of The category "Other"**

| Study / Patient ID | Table S11: AI/Placebo-Treated Patients in All Studies Who Dropped Out for "Other Reasons" | |
|---|---|---|
| | Study Arm | Reasons given by patients descibed as "Other" include: |
| **Study 005** | | |
| 008205 | **75mg AI BID** | Misunderstood requirement to roll over to AI 006 protocol on D29; not Day 56 |
| 008229 | √ | Patient enrolled in study 006 directly instead of being enrolled from study 005 |
| 104154 | √ | Social/medical situations precluded compliance with appt.; asthma/CF exacerbations. |
| 195327 | √ | Subject had taken a prohibited medication |
| | | |
| 061235 | **Placebo BID** | Tired of frequent visits; CF-related Diabetes newly diagnosed: felt worried/depressed |
| | | |
| 146276 | **75mg AI TID** | Pre-op Pulmonary treatment for sinus surgery; Bronchiectasis on chest x-ray. |
| | | |
| **Study 007** | | |
| 014514 | **Placebo TID** | Met exclusion criterion of being on antipseudomonal antibiotic during the study. |
| 044493 | √ | Was on Azithromycin every Monday, Wednesday and Friday |
| 152495 | √ | Patient requested ending participation in the study. |
| | | |
| **Study 003** | | No category of "other" reason for discontinuation in study 3 |
| | | |
| **Study 006** | | |
| 005316 | **75mg AI BID** | Withdrew consent |
| 061256 | √ | Patient had extended future travel plans and could not attend study visits |
| 104153 | √ | Positive pregnancy test at visit 14 |
| 111175 | √ | Poor compliance with study drug for visits 2 and 4; then, lost to follow-up |
| | | |
| 005402 | **75mg AI TID** | Withdrew consent |
| 197309 | √ | Withdrew consent and refused to come back for end of study visit |

**√ = Same as above; appt. = appointment**

## Dropouts /Discontinuations: Phase 1 studies

**Study 001:** No subject was withdrawn from the trial because of an adverse event. An AE of cough led to discontinuation of the study medication in one subject who still continued in the trial and completed all trial assessments.

**Study 002:** Three patients had AEs that led to discontinuation of study drug (one patient in each treatment dose). An additional four patients were discontinued from the study as a result of an AE (one patient in the placebo group, two patients in the 75 mg AI group, and one patient in the 225 mg AI group). None of the AEs leading to discontinuation was considered to be related to the trial drug.

### *7.3.4 Significant Adverse Events*

No major or significant AEs considered potentially debilitating emerged from the study results reviewed for this NDA. Cough and productive cough were the most common. However, they occurred in AI-treated and placebo-treated patients with similar frequencies in the different studies conducted for the NDA.

### *7.3.5 Submission Specific Primary Safety Concerns*

As stated under section 7.3.4, no primary safety concern specific and unique to AI emerged during the review of various studies. In sifting through the database of this NDA, most of the AEs reported by study patients who received AI were also reported by patients who received only placebo. In many instances, the incidence occurred at similar rates in AI and placebo study arms. In others, the AEs occurred at higher rates in the placebo arm than in the AI arm, particularly in the TID regimen – the to-be-marketed AI regimen. Cough, productive cough, and dyspnoea (whether exertional or exacerbated) are AEs associated with CF and generally expected in the course of treatment of the disease or during an exacerbation. Decreased pulmonary function testing was also recorded as an SAE in this submission. This is also a feature of CF disease and is often encountered in the course of treatment of the disease.

## 7. 4 Supportive Safety Results

### *7.4.1 Common Adverse Events*

Table S11a shows the most common treatment emergent AEs (TEAEs) reported by ≥ 5% of study patients in any arm of the studies. The TEAEs are listed in order of frequency according to the TID arm. The less commonly reported AEs are listed in aphabetical order in 6 tables (S11b through S11g) in appendix 1.
As shown in table S11a, cough, productive cough, nasal congestion, and dyspnea were among the five most commonly reported TEAEs by study patients. Among these five most commonly reported TEAEs in the BID arm, abdominal pain was reported at a higher rate (20.3%) in the AI treatment arm than in the placebo arm (7.9%). Otherwise, these reported TEAE rates among the top five most reported TEAEs were generally comparable across study arms in both BID and TID arms. Among the other TEAEs reported less frequently than these five, pharyngolaryngeal pain was also reported at a higher rate (17.4 %) among the AI BID-treated patients compared to 7.9% among placebo-treated patients in those who received BID regimen. Among the patients who received TID regimen, the frequencies of the same TEAE were comparable across study arms.

## Common TEAEs Reported by ≥ 5% of Studies 005 and 007 Patients (in Any Study Arm)

| **Table S11a:** | **Number (%) of TEAEs Reported in Study 005 and 007 Patients** | | | |
|---|---|---|---|---|
| | **Phase 3 Double–Blind Studies** | | | |
| | **Pooled Study 007 & Study 005 (TID Arms Only)** | | **Study 005 (BID Arms Only)** | |
| **TEAEs (Preferred term)** | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Cough | 82 (56.2) | 68 (55.7) | 52 (75.4) | 26 (68.4) |
| Productive cough | 45 (30.8) | 45 (36.9) | 26 (37.7) | 14 (36.8) |
| Dyspnoea (including exacerbated) | 31 (21.2) | 32 (26.2) | 13 (18.8) | 8 (21.1) |
| Nasal congestion | 25 (17.1) | 18 (14.8) | 24 (34.8) | 11 (28.9) |
| Pharyngolaryngeal pain | 23 (15.8) | 16 (13.1) | 12 (17.4) | 3 (7.9) |
| Wheezing | 24 (16.4) | 14 (11.5) | 10 (14.5) | 4 (10.5) |
| Crackles lung | 20 (13.7) | 20 (16.4) | 6 (8.7) | 3 (7.9) |
| Pyrexia | 19 (13.0) | 10 (8.2) | 9 (13.0) | 2 (5.3) |
| Headache | 17 (11.6) | 15 (12.3) | 8 (11.6) | 3 (7.9) |
| Headache | 17 (11.6) | 15 (12.3) | 8 (11.6) | 3 (7.9) |
| Rhinorrhoea | 17 (11.6) | 13 (10.7) | 8 (11.6) | 3 (7.9) |
| Respiratory tract congestion | 16 (11.0) | 18 (14.8) | 9 (13.0) | 4 (10.5) |
| Haemoptysis | 16 (11.0) | 14 (11.5) | 8 (11.6) | 6 (15.8) |
| Abdominal pain | 15 (10.3) | 10 (8.2) | 14 (20.3) | 3 (7.9) |
| Fatigue | 15 (10.3) | 16 (13.1) | 9 (13.0) | 5 (13.2) |
| Chest discomfort | 13 (8.9) | 8 (6.6) | 9 (13.0) | 3 (7.9) |
| Sinus congestion | 10 (6.8) | 8 (6.6) | 2 (2.9) | 3 (7.9) |
| Vomiting | 10 (6.8) | 5 (4.1) | 4 (5.8) | 2 (5.3) |
| Pulmonary function test decreased | 9 (6.2) | 10 (8.2) | 3 (4.3) | 3 (7.9) |
| Nausea | 8 (5.5) | 4 (3.3) | 4 (5.8) | 2 (5.3) |
| Diarrhoea | 7 (4.8) | 3 (2.5) | 8 (11.6) | 1 (2.6) |
| Throat irritation | 6 (4.1) | 3 (2.5) | 2 (2.9) | - |
| Exercise tolerance decreased | 5 (3.4) | 12 ( 9.8) | 6 (8.7) | 3 (7.9) |
| Sinus headache | 5 (3.4) | 3 (2.5) | 5 (7.3) | 1 (2.6) |
| Non-cardiac chest pain | 4 (2.7) | 5 (4.1) | 3 (4.3) | 4 (10.5) |
| Postnasal drip | 3 (2.1) | 2 (1.6) | 6 (8.7) | 2 (5.3) |
| Decreased appetite | 2 (1.4) | 9 (7.4) | 9 (13.0) | 3 (7.9) |
| → = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified<br>↑ ALT = Alanine aminotransferase increased; ↑ AST = Aspartate aminotransferase increased | | | | |

***MO's Comments:*** *Abdominal/ pharyngolaryngeal pain were reported at higher rates among the five most commonly reported TEAEs in patients who received AI BID regimen than in those who received placebo. While the higher rate of pharyngolaryngeal pain may be explained as probably due to an irritating effect of AI in the upper airway during inhalation of the product, the reason for the frequency of abdominal pain in AI-treated patients is less clear. Other less reported TEAEs with higher rates of reporting in the AI arm included pyrexia, chest discomfort, decreased appetite, and diarrhea (all written in blue text).*

*The other TEAEs in the BID arm were reported at generally similar rates in both study arms. Among the group of patients who received TID (theto-be-marketed) regimen, the reporting rates of TEAEs were either similar across study arms or were higher in the placebo arm than in the AI-treated study patients. The rest of the TEAEs are listed in tables S11b through S11g [appendix 1].*

**Treatment-Related AEs [TRAEs] among Studies 005 and 007 Patients**
Table S12a lists the most common TRAEs among studies 005 and 007 patients. The rest of the TRAEs are listed in tables S12b and S12c in appendix 1.

The rates of most TRAEs were either similar across study arms or were higher in the placebo arm. Where the rates were higher in the AI-treated patients, the rates are written in blue text in the table. Accordingly, while cough, dyspnoea, chest discomfort, productive cough, and wheezing were the five most commonly reported TRAEs in the two studies, among the patients who received the AI TID treatment 25/146 (17.1%) reported a TRAE of cough which was about twice the rate reported in placebo-treated patients [i.e., 10/122 (8.2%)].
Reporting rates of chest discomfort among patients that received the TID regimen was slightly higher in AI-treated patients than placebo-treated patients but the patient numbers involved were small.

**Treatment-Related AEs [TRAEs] among Studies 005 and 007 Patients**

| **Table S12a:** | **Number (%) of TRAEs Reported in Study 005 and 007 Patients** | | | |
|---|---|---|---|---|
| | **Phase 3 Double –Blind Studies** | | | |
| | **Pooled Study 007 & Study 005 (TID arms Only)** | | **Study 005 (BID Arms Only)** | |
| **AEs (Preferred term)** | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| | | | | |
| Cough | 25 (17.1) | 10 (8.2) | 12 (17.4) | 7 (18.4) |
| Dyspnoea (including execerbated) | 6 (4.1) | 6 (4.9) | 2 (2.9) | 3 (7.9) |
| Chest discomfort | 6 (4.1) | 2 (1.6) | 1 (1.4) | - |
| Productive cough | 4 (2.7) | 7 (5.7) | - | 4 (10.5) |
| Wheezing | 4 (2.7) | 5 (4.1) | 3 (4.3) | - |
| Pharyngolaryngeal pain | 4 (2.7) | 3 (2.5) | 2 (2.9) | 1 (2.6) |
| Throat irritation | 3 (2.1) | 2 (1.6) | 1 (1.4) | - |

***MO's Comment:*** *The higher reporting rate of cough among AI TID-treated patients could have been related to the potential for upper (and lower?) airway irritation associated with the receipt of nebulized AI three times daily. The phenomenon showed no consistency with BID-treated patients given the comparable rates of occurrence in the patients who received AI or placebo BID. The occurrence of chest discomfort may be related to treatment but the numbers reporting this event is much smaller.*

**Patients Reporting TEAEs by Severity in studies 005 and 007**

Table S13 shows the number (and percentages) of patients in studies 005 and 007 who reported the severity of their TEAEs (and TRAEs). Symptoms were characterized as mild, moderate or severe. As shown in the table, most of the AEs were reported as mild or moderate. Each patient in some cases reported multiple TEAEs or TRAEs. The severity of symptoms sometimes shifted from one degree to another in the same patient, according to symptom or study visit.Thus more symptoms and severity types were reported in greater numbers than the number of patients participating in the studies. Among patients who received BID regimen, 20/69 (29%) who received AI reported severe TEAEs compared to 3/38 (7.9%) in the placebo arm. In the TID regimen, the rates of severe TEAEs were the same for AI and placebo. Mild and moderate TEAEs and TRAEs are generally comparable. No regimen differences were apparent.

**TEAE/TRAE duration:** For patients who received AI treatment, their TEAEs generally resolved in a median duration of 13 days while the TEAEs in placebo-treated patients resolved in a median duration of 15 days (TID). For patients whose AEs were considered treatment-related, their TRAEs resolved in a median duration of 9 days in patients who received AI treatment (TID and BID) whereas TRAEs in patients who received placebo resolved in a median duration of 15 days.

| **Table S13** | **Number (%) of Patients Reporting TEAEs by Severity and Relationship to Study Drug -007 & 005** | | | | |
|---|---|---|---|---|---|
| **Severity** | | 75 mg TID N = 146 | Placebo TID N = 122 | 75 mg BID N = 69 | Placebo BID N = 38 |
| Mild | TRAE - n (%) | 41 (28.1) | 19 (15.6) | 17 (24.6) | 14 (36.8) |
| | TEAE - n (%) | 104 (71.2) | 88 (72.1) | 61 (88.4) | 29 (76.3) |
| | | | | | |
| Moderate | TRAE - n (%) | 16 (11) | 15 (12.3) | 7 (10.1) | 8 (21.1) |
| | TEAE - n (%) | 95 (65.1) | 80 (65.6) | 52 (75.4) | 28 (73.7) |
| | | | | | |
| Severe | TRAE - n (%) | 2 (1.4) | 1 (0.8) | 4 (5.8) | 1 (2.6) |
| | TEAE - n (%) | 24 (16.4) | 20 (16.4) | 20 (29) | 3 (7.9) |
| Total № of patients reporting TEAEs/ TRAEs [n/n] | | 128/98 | 103/ 28 | 66/21 | 35/14 |

**The Most Common TEAEs (Reported by ≥ 10 % of Patients in Any Study Arm) in Study 003**

As a result of the relative small number of patients that participated in this double-blind Phase 2 study 003, the reported TEAEs involved a correspondingly small number of patients by comparison to Phase 3 studies. The key object of this study was to explore for emergence of dose-related safety potential of AI.

As in double-blind Phase 3 (studies 005 and 007) patients, and as shown in table S14a, cough was the most common TEAE in study 003 and occurred with comparable frequencies across all three study arms. Although headache and pyrexia appeared to have slightly increasing

frequencies according to dose, the numbers of patients were too small to draw meaningful conclusions regarding a relationship between dose and frequencies of these TEAEs. The other TEAEs reported in this study are listed in alphabetical order in tables S14b through S14d under appendix 1.

**TEAEs in study 003**

| **Table S14a:** | **Number (%) of patients reporting TEAEs in study 003** | | |
|---|---|---|---|
| | **Phase 2 Double –Blind Study** | | |
| **AEs (Preferred term)** ⇓ | 225 mg BID N = 37 | 75 mg BID N = 37 | Placebo BID N = 31 |
| Cough | 13 (35.1) | 12 (32.4) | 12 (38.7) |
| Headache | 6 (16.2) | 4 (10.8) | 2 (6.5) |
| Pyrexia | 5 (13.5) | 3 (8.1) | 2 (6.5) |
| Nasal congestion | 5 (13.5) | 1 (2.7) | 6 (19.4) |
| Productive cough | 4 (10.8) | 7 (18.9) | 5 (16.1) |
| Rhinorrhoea | 4 (10.8) | 3 (8.1) | 3 (9.7) |
| Nasal mucosal disorder | 4 (10.8) | 3 (8.1) | 3 (9.7) |
| Chest discomfort | 4 (10.8) | 3 (8.1) | - |
| Sinus congestion | 4 (10.8) | 3 (8.1) | - |
| Dysgeusia | 4 (10.8) | 1 (2.7) | - |
| Pharyngolaryngeal pain | 3 (8.1) | 5 (13.5) | 3 (9.7) |

***MO's Comment:*** *Most of the TEAEs occurred at comparable rates across study arms. The numbers of patients involved in the three arms are not enough to make any strong conclusions regarding a relationship between dose received and occurrrence of headache or pyrexia. With regard to nasal congestion, its frequency rate was higher in the placebo arm than any of the other two arms. The rationale for not using a higher dose than 75 mg for Phase 3 studies was discussed earlier in the review under subsections 7.2.1 and 7.2.2.*

**TRAEs among Study 003 Patients**

Table S15 displays all the treatment-related AEs in study 003. Cough was the most TRAE reported in this study, consistent with patients in studies 007 and 005. It occurred at a slightly higher rate among patients in 225 mg BID arm than in placebo-treated patients. The frequency rate of this TRAE in patients who received 75 mg BID was 13.5 %, i.e. between the rates in the other two arms. The other TRAEs are shown in the same table S15.

## TRAEs among Study 003 Patients

| **Table S15:** | **Number (%) of patients reporting TRAEs in study 003** | | |
|---|---|---|---|
| | **Phase 2 Double –Blind Study** | | |
| **AEs (Preferred term)** | 225 mg BID | 75 mg BID | Placebo BID |
| ⇓ | N = 37 | N = 37 | N = 31 |
| Abdominal pain upper | - | 1 (2.7) | - |
| Chest discomfort | 3 (8.1) | 3 (8.1) | - |
| Chest pain | 1 (2.7) | - | - |
| Conjunctival hyperaemia | - | 1 (2.7) | - |
| Cough | 7 (18.9) | 5 (13.5) | 3 (9.7) |
| Crackles lung | 1 (2.7) | - | 1 (3.2) |
| Dizziness | - | 1 (2.7) | 1 (3.2) |
| Dysgeusia | 4 (10.8) | 1 (2.7) | - |
| Dyspnoea | 2 (5.4) | 1 (2.7) | - |
| Ear pain | 1 (2.7) | - | - |
| Fatigue | 2 (5.4) | 1 (2.7) | 1 (3.2) |
| Glossodynia | - | 1 (2.7) | - |
| Haemoptysis | 1 (2.7) | - | - |
| Headache | 2 (5.4) | 1 (2.7) | - |
| Hoarseness | 1 (2.7) | 2 (5.4) | - |
| Joint swelling | 1 (2.7) | - | - |
| Loose stools | 1 (2.7) | - | - |
| Lymphadenopathy | - | 1 (2.7) | - |
| Musculoskeletal chest pain | 1 (2.7) | - | - |
| Nasal congestion | 1 (2.7) | 1 (2.7) | - |
| Nasal mucosal disorder | 1 (2.7) | 1 (2.7) | - |
| Nausea | - | 1 (2.7) | 1 (3.2) |
| Oral candidiasis | 1 (2.7) | - | - |
| Pain | - | 1 (2.7) | - |
| Paranasal sinus hypersecretion | 1 (2.7) | - | - |
| Pharyngeal erythema | 1 (2.7) | 1 (2.7) | - |
| Pharyngolaryngeal pain | 1 (2.7) | 1 (2.7) | 1 (3.2) |
| Productive cough | 2 (5.4) | - | 2 (6.5) |
| Pyrexia | 1 (2.7) | 2 (5.4) | 1 (3.2) |
| Rash | - | 1 (2.7) | - |
| Rhinorrhoea | 1 (2.7) | - | - |
| Throat irritation | - | 1 (2.7) | 1 (3.2) |
| Tongue disorder | - | 1 (2.7) | - |
| Urticaria | - | 1 (2.7) | - |
| Vomiting | - | 1 (2.7) | 1 (3.2) |
| Wheezing | 3 (8.1) | 1 (2.7) | 1 (3.2) |

***MO's Comment:*** *Aside from cough and dysgeusia as shown in the above table (S15) in blue text, no dose-related TRAEs are apparent. Even with the two AEs mentioned, the differences in frequencies are slight, not dramatic. But the database is relatively small and the numbers of patients with the two AEs are not large.*

**The Most CommonTEAEs (Reported by ≥ 10 % of Patients in Any Study Arm) - Study 006**

Per table S16a, cough and productive cough were the most commonly reported AEs. The rest are listed in order of frequencies. The TEAEs written in blue text (productive cough, decreased appetite, and sinus congestion) were reported at higher rates in patients receiving TID regimen than in patients in the BID arm (see table). The frequency rates of the rest of the TEAEs are fairly comparable across study arms. Other TEAEs reported at lower frequency rates are listed in tables S16b through S16j in appendix 1.

| **Table S16a** | **Number (% ) ≥ 10 % of patients reporting TEAEs in study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg TID N = 125** | **75 mg BID N = 82** |
| Cough | 101 (80.8) | 64 (78) |
| Productive cough | 84 (67.2) | 40 (48.8) |
| Respiratory tract congestion | 50 (40.0) | 29 (35.4) |
| Exercise tolerance decreased | 49 (39.2) | 29 (35.4) |
| Pharyngolaryngeal pain | 45 (36.0) | 35 (42.7) |
| Fatigue | 41 (32.8) | 27 (32.9) |
| Decreased appetite** | 41 (32.8) | 18 (22.0) |
| Dyspnoea (including exacerbated and exertional Dyspnoea) | 39 (31.2) | 21 (25.6) |
| Pyrexia | 37 (29.6) | 29 (35.4) |
| Nasal congestion | 36 (28.8) | 28 (34.1) |
| Haemoptysis | 27 (21.6) | 20 (24.4) |
| Headache | 25 (20.0) | 18 (22.0) |
| Non-cardiac chest pain | 17 (13.6) | 13 (15.9) |
| Abdominal pain (including upper and lower) | 19 (15.2) | 17 (20.7) |
| Crackles lung ** | 15 (12.0) | 17 (20.7) |
| Chest discomfort | 20 (16.0) | 15 (18.3) |
| Rhinorrhoea | 27 (21.6) | 15 (18.3) |
| Wheezing | 23 (18.4) | 14 (17.1) |
| Vomiting | 14 (11.2) | 14 (17.1) |
| Nausea | 15 (12.0) | 10 (12.2) |
| Arthralgia | 11 (8.8) | 10 (12.2) |
| Diarrhoea | 12 (9.6) | 9 (11.0) |
| Pulmonary function test decreased | 15 (12.0) | 6 (7.3) |
| Sinus congestion | 20 (16.0) | 6 (7.3) |
| Sinus headache | 14 (11.2) | 7 (8.5) |
| Weight decreased | 11 (8.8) | 12 (14.6) |

**The Most Common TRAEs - Study 006**

Table S17a shows the most common TRAEs in study 006. Aside from respiratory tract congestion reported by 6/125 (4.8%) in the TID arm compared to none in the BID arm TRAEs were reported in comparable frequency rates in the two regimen arms. The less frequently reported TRAEs in study 006 are listed in tables S17b and S17c in appendix 1.

**The Most Common TRAEs in Study 006**

| **Table S17a** | **Number (%) of patients reporting AEs in study 006** | |
|---|---|---|
| | **75 mg TID** | **75 mg BID** |
| **AEs preferred term** | **N = 125** | **N = 82** |
| Cough | 22 (17.6) | 14 (17.1) |
| Haemoptysis | 8 (6.4) | 7 (8.5) |
| Dyspnoea | 7 (5.6) | 2 (2.4) |
| Chest discomfort | 6 (7.3) | 4 (4.9) |
| Respiratory tract congestion | 6 (4.8) | - |
| Productive cough | 5 (4.0) | 3 (3.7) |
| | | |

***MO's Comment:*** *It is unclear why 6 patients reported respiratory tract congestion in the TID arm versus none in the BID arm. It is generally not an unusual AE in CF patients regardless of drug, dose or regimen received. Some of these repiratory symptoms (e.g. respiratory tract congestion, pulmoary congestion, rhinorrhea, nasal congestion, rhinitis, etc) tend to overlap in CF patients AE reporting. Nevertheless, it is interesting that it was not reported as a TRAE in patients who received BID dose in study 006 but was reported in comparable frequencies in studies 005 and 007 (table S11a).*

**Patients Reporting TEAEs by Severity in Study 006**

Table S18 diplays the number (and percent) of patients in study 006 who reported the severity of their TEAEs as well as their TRAEs. As in the other phase 3 studies, symptoms were characterized as mild, moderate or severe. Most of the AEs were reported as mild, or moderate in in severity as shown in table S18. Only a small number of patients reported their AEs as severe. As in other studies, many patients reported multiple TEAEs or TRAEs, some of which were described as mild on one occasion and moderate on another visit – i.e., the severity of symptoms sometimes shifted from one degree to another in the same patient, according to symptom or study visit.Thus more symptoms and severity types were reported in greater numbers than the number of patients participating in the studies.
The TEAEs generally resolved in a median duration of 14 days in TID arm, and 13 days in the BID arm patients. Among patients with TRAEs, their AEs resolved in a median duration of 6 days in the TID arm, and 5 days in the BID arm patients.
The symptom severity reporting rates were comparable across study arms. No regimen differences were apparent.

**Number (%) of Patients Reporting TEAEs by Severity and Relationship to Study Drug –Study 006**

| **Table S18** | **Number (%) of Patients Reporting TEAEs by Severity and Relationship to Study Drug** | | |
|---|---|---|---|
| **Severity** | | 75 mg TID N = 125 | 75 mg BID N = 82 |
| Mild | TRAE - n (%) | 39 (31.2) | 24 (29.3) |
| | TEAE - n (%) | 110 (88.0) | 75 (91.5) |
| | | | |
| Moderate | TRAE - n (%) | 18 (14.4) | 8 (9.8) |
| | TEAE - n (%) | 92.(73.6) | 57 (69.5) |
| | | | |
| Severe | TRAE - n (%) | 3 (2.4) | 1 (1.2) |
| | TEAE - n (%) | 13 (10.4) | 10 (12.2) |
| Total № of patients reporting TEAEs/ TRAEs [n/n] | | 115 (92.0)/ 47(37.6) | 79 (96.3) /25 (30.5) |

## Microbiological Safety in Study 006

The following summarizes the experiences of patients that participated in study 006 regarding changes in *PA* susceptibilities while they received multiple cycles of AI.

**Over the first 3 treatment courses from Visit 1 for all *PA* isolates**

- Majority of patients continued to have positive sputum cultures for *PA*.
- At Visit 1, the percentage of patients with MIC > 8 µg/mL for *PA* isolate with the highest MIC was 41% for the BID regimen and 45% for the TID regimen.
- The largest increase in the percentage was to 60% in the BID regimen at the end of the off-treatment interval after the third treatment course and to 56% at completion of the third treatment course in the TID regimen.
- There was no consistent trend in the percentage of patients with the highest MIC over the time interval during the first three treatment courses.
- There were no notable increases in the $MIC_{50}$ or $MIC_{90}$ of any of the other antibiotics tested against *PA* after treatment with AI.

**After six courses of AI Treatment in Study 006 [Sponsor's Subsequent Report]**

The Sponsor provided some microbiological information (though not submitted to the NDA) describing the experiences of study 006 patients after they had received six cycles of AI treatment. In this later report, the Sponsor explained that the tracking of microbiological trends following receipt by study patients of multiple cycles of AI was to ascertain the potential for the development of antibiotic resistance and emergence of other pathogens. According to the report, overall, no changes in the susceptibility of *PA* to aztreonam or to other antibiotics, including aminoglycosides, quinolones, and beta-lactams, were observed after up to six 28-day courses (with 28 days between courses) of

AI in the open-label follow-on study. In addition, a trend toward increased tobramycin susceptibilty was observed. This latter trend was interpreted by the Sponsor as a reflection of the activity of AI against tobramycin-resistant *PA* isolates. The Sponsor also reported that no trends in the treatment-emergent isolation of other bacterial respiratory pathogens, including *B. cepacia, S. maltophila, A. xylosoxidans, and S. aureus*, were observed after up to six 28-day courses of AI in the open-label follow-on study.

## TEAEs in Phase 1 studies

The following summarizes the TEAEs experienced by Phase 1 subjects and patients.

As reported earlier in the review, neither death nor SAEs were reported in any of the two Phase 1 studies.

**Study 001:** This study was conducted in 24 healthy adults. The objectives included an assessment of safety, tolerability and pharmacokinetics of AI. The TEAEs reported in study 001 included headache (in a subject who received 95 mg) and dizziness (in another subject who received 190 mg). Dysgeusia and cough were two drug-related AEs experienced from the receipt of 285 mg in the course of the study. These AEs were considered mild to moderate and resolved before the end of the study. While the cough necessited discontinuation of study medication, it did not lead to the withdrawal of the patient from the study.

**Study 002:** Table S18.5 comes from study 002 (Phase 1) cohort study alone (also see table G2). These CF patients were exposed to each dose of AI (shown in the table), i.e. the same group receiving different dose at a time (separated with a washout period), except the 12 patients who received placebo. This study was conducted in 35 CF patients (which included 18 adults and 17 pediatric patients, thirteen to 17 years old). All TEAEs in study 002 are as shown in table S18.5 by treatment groups. All adverse events resolved before the end of the trial. The adverse event of cough led to discontinuation of study medicationmedication, although the subject continued in the trial and completed all trial assessments.

**Modified Sponsor's Table 11.6: Adverse Events by Treatment Group in Study 002 (Phase 1)**

| **Table S18.5** | **Number (%) reporting TEAEs in study 002** | | | |
|---|---|---|---|---|
| **Reported TEAEs (Preferred Term)** | **225 mg AI (N = 22)** | **150 mg AI (N =23)** | **75 mg AI (N = 23)** | **Placebo (N = 12)** |
| Abdominal tenderness | 1 (4.5) | - | - | - |
| Chest pain | - | 1 (4.3) | - | 1 (8.3 ) |
| Chest tightness | 1 (4.5) | 2 (8.7) | 1 (4.3) | - |
| Sinusitis NOS | 1 (4.5) | - | - | - |
| Headache | 2 (9.1) | - | - | 1 (8.3 ) |
| Heart rate increased | 1 (4.5) | 1 (4.3) | 1 (4.3) | - |
| Pulmonary function test NOS decreased | - | 1 (4.3) | - | - |
| Cough | - | - | 1 (4.3) | - |
| Cough aggravated | 4 (18.2) | 1 (4.3) | 1 (4.3) | - |
| Crackles lung | - | 1 (4.3) | 2 (8.7) | 1 (8.3 ) |
| Epistaxis | 1 (4.5) | - | - | - |
| Nasal congestion | 1 (4.5) | 1 (4.3) | 1 (4.3) | - |
| Nasal Edema | 1 (4.5) | - | - | - |
| Pharyngeal erythema | 1 (4.5) | - | - | 1 (8.3 ) |
| Pharyngitis | - | 1 (4.3) | - | - |
| Rhinorrhoea | 1 (4.5) | - | - | - |
| Sputum increased | 2 (9.1) | - | 1 (4.3) | - |
| Wheezing | - | 1 (4.3) | 1 (4.3) | 1 (8.3 ) |

NOS = Not otherwise specified

### *7.4.2 Laboratory Findings*

### Hematology

Table S19 shows the number (and percentages) of patients in studies 007 and 005 who developed hematologic abnormalities while participating in the studies. Tables S20 and S21 also show patients with hematologic laboratory abnormalities in study 003 and 006 respectively.

In table S19, like the other two tables, hematology indices evaluated (on the left side of each table) for this review were listed. The number (and percentages) of patients with abnormal laboratory values of WBC, hematocrit, platelets, and eosinophils were listed. These were patients whose shifts in their laboratory values (below or above normal range) occurred following the receipt of study treatment. In general, laboratory assessments during the trials were performed according to pre-scheduled visits as outlined in the study designs under section 6.1.1 for studies 007 and 005.

**Leukocytosis and Leukopenia**
Using the upper limit of WBC as 11 x $10^3/mm^3$, leukocytosis, as shown in table S19, occurred at comparable rates in patients who received either AI or placebo. The elevated WBCs probably

represented acute inflammatory changes related to underlying CF chronic lung disease. Leukopenia only involved three patients, one in each arm - with the exception of the placebo TID arm.
The lowest WBC count occurred in a patient in study 007 who received AI TID. The WBC dropped from a baseline value of 9.08 x $10^3$/$mm^3$ to 3.06 x $10^3$/$mm^3$ on day 28, i.e., the end of AI therapy. By day 42, the WBC had only improved slightly to 3.41. There were no addtional follow-up values to ascertain time to resolution. While this case was noteworthy, there was no significant number of such cases, or an emerging pattern. Accordingly, the reviewer did not explore any further.

**Other Hematologic Indices Assessed**

Anemia, eosinophilia, or thrombocytopenia was not reported at such rate imbalances that merited further exploratiion by the reviewer either. The rates for these indices are as shown in Table S19.

**Hematology Findings in Study 005 and 007 Patients**

| **Table S19** | **Number (%) of patients with hematologic abnormalities in Studies 005 and 007** | | | |
|---|---|---|---|---|
| | **Pooled Study 007 & Study 005 (TID arms Only)** | | **Study 005 (BID Arms Only)** | |
| **AEs (Preferred term)** | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| **Leukocytosis (WBC >11 x $10^3$/$mm^3$)** | | | | |
| Normal BL: Increase on treatment | 9 (6.2) | 5 (4.1) | 5 (7.2) | 4 (10.5) |
| High BL: Increase on treatment | 5 (3.4) | 5 (4.1) | 5 (7.2) | - |
| Combined | 14 (9.6) | 10 (8.2) | 10 (14.5) | 4 (10.5) |
| **Leukopenia (WBC <4.0 x $10^3$/$mm^3$)** | | | | |
| Normal BL: Decrease on treatment | 1 (0.7) | - | 1 (1.4) | 1 (2.6) |
| **Eosinophilia** | | | | |
| Normal BL: Increase on treatment | 3 (2.1) | 2 (1.6) | - | - |
| **Anemia (HCT < 35)** | | | | |
| Normal BL: Decrease on treatment | 1 (0.7) | 1 (0.8) | - | 1 (2.6) |
| **Thrombocytopenia (Plt < 100K/ $mm^3$)** | | | | |
| > than $10^5$ at BL: Decrease on treatment | 2 (1.4) | - | 1 (1.4) | - |
| **Pancytopenia** | - | - | - | - |

BL= Baseline; HCT = Hematocrit; WBC= White Blood Cell Count; Plt = Platelet); - = no value;

***MO Comments:*** *Most patients experienced no significant shifts in their hematologic results in studies 007 and 005. Only a few patients who had normal baseline hematologic laboratory values experienced shifts in either direction that were of some significance while receiving treatment. Other patients had abnormal baseline values that worsened in the course of treatment. But no discernable pattern emerged to warrant further elucidation. There were no outlier cases that were distinct enough to be marked as potentially significant. No regimen-related abnormalities were apparent. There seemed to be a trend in the direction of recovery.*

**Hematology Findings in Study 003 Patients**

| **Table S20** | **Number (%) of patients with hematologic abnormalities in Study 003** | | |
|---|---|---|---|
| | **Phase 2 Double –Blind Study** | | |
| **AEs (Preferred term)** | 225 mg BID | 75 mg BID | Placebo BID |
| ⇓ | N = 37 | N = 37 | N = 31 |
| **Leukocytosis ( WBC >11 x $10^3$)** | | | |
| Normal BL: Increase on treatment | 1 (2.7) | 1 (2.7) | 1 (3.2) |
| High BL: Increase on treatment | 2 (5.4) | 1 (2.7) | 2 (6.5) |
| | | | |
| **Leukopenia (WBC <4.0 x $10^3$)** | | | |
| Normal BL: Decrease on treatment | - | - | - |
| | | | |
| Eosinophilia | | | |
| Normal BL: Increase on treatment | - | 3 (8.1) | - |
| | | | |
| **Anemia (HCT < 35)** | | | |
| Normal BL: Decrease on treatment | - | - | - |
| | | | |
| **Thrombocytopenia (Plt count < $10^5$/mL )** | | | |
| Normal BL: Decrease on treatment | - | 1 (2.7) | - |
| | | | |
| **Pancytopenia** | - | - | - |

BL= Baseline; HCT = Hematocrit; WBC= White Blood Cell Count; Plt = Platelet); - = no value;

***MO Comments:*** *Leukocytosis occurred with comparable incidence across all three arms as shown in the table (S20). Why eosinophilia would occur in isolation in the three patients who received AI BID treatment, with no reported similar events in the other two arms, particularly in*

*the 225 mg dose arm, is unclear. Neither leukopenia nor anemia within the parameters stated was reported in study 003.*

**Hematology Findings in Study 006 Patients**

| **Table S21** | **Number (%) of patients with hematologic abnormalities in Study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg TID N = 125** | **75 mg BID N = 82** |
| | | |
| **Leukocytosis ( WBC >11 x $10^3$)** | | |
| Normal BL: Increase on treatment | 17 (13.6) | 11 (13.4) |
| High BL: Increase on treatment | 8 (6.4) | 3 (3.7) |
| Combined | 25 (20.0) | 14 (17.1) |
| | | |
| | | |
| **Leukopenia ( WBC <4.0 x $10^3$)** | | |
| Normal BL: Decrease on treatment | 2 (1.6) | 1 (1.2) |
| | | |
| Eosinophilia | | |
| Normal BL: Increase on treatment | 9 (7.2) | 6 (7.3) |
| | | |
| **Anemia (HCT < 35)** | 9 (7.2) | 1 (1.2) |
| Normal BL: Decrease on treatment | | |
| | | |
| **Thrombocytopenia (Plt count < $10^5$/mL)** | - | - |
| Normal BL: Decrease on treatment | | |
| | | |
| **Pancytopenia** | - | - |
| | | |

***MO Comments:*** *The apparently regimen-related incidence of anemia suggested in the above table among the patients in the open label study 006 is not consistent with the experience of the patients in the double-blind studies 007 and 005. Study 003 only had BID arms and patients received AI for 14 days – although patients in one arm received AI at 225 mg BID. No anemia (as defined by the parameter stated) was reported or documented.*

## Hematology Findings in Phase 1

Per the Sponsor, no clinically relevant shifts occurred in mean values for any parameter evaluated in Phase 1 subjects/patients. They reported that one adolescent patient's neutrophils

shifted from normal to high (Patient 030-3); the white blood cell counts of three other patients (030-3, 076-3 and 027-4) also shifted from normal to high. But the changes were reported as clinically insignificant.

## Serum Chemistry

The following constitute the significant serum chemistry assessments performed during study visits: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, gamma glutamyl tranferase (GGT); glucose, blood urea nitrogen (BUN) and creatinine. Per the Sponsor, repeat testing of clinically significant abnormal laboratory (lab) values was required for:

• AST or ALT > 5 times upper limit of normal or
• Serum creatinine > 2 times upper limit of normal for age

Also, clinically significant changes (as assessed by the investigator) in laboratory values were considered AEs and were to be re-tested by or at the next scheduled visit.

Despite the statement made by the Sponsor above about requiring repeat testing for lab values for ALT or AST > 5 times upper limit of normal (ULN), table S22a and table S22b were drawn merely to show the Sponsor's failure to be consistent with the above statement with regards to ALT or AST elevation at the level stated by the Sponsor. See MO comments below table S22b.

**Patients with high (> 3x ULN) ALT/AST values during visits - Study 005**

| **Table S22a** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient ID number** | **Liver Enzyme** | **Normal Range For Lab.** | **Screening Day - 42** | **Visit 2 Day -28** | **Visit 3 Day 0** | **Visit 4 Day 14** | **Visit 5 Day 28** | **Visit 6 Day 42** | **Dose received** |
| | | | | | | | | | |
| **104360 §** | **ALT** | **6 - 34** | **71** | | **143** | | **99** | **112** | **75mg AI BID** |
| | **AST** | **9 - 34** | **31** | | **51** | | **147** | **224** | |
| | | | | | | | | | |
| **401138** | **ALT** | **6 - 43** | **268** | | **22** | | **26** | **24** | **75mg AI TID** |
| | **AST** | **10 - 40** | **406** | | **26** | | **25** | **30** | |
| | | | | | | | | | |

ID = identification; ALT = alanine aminotransferase; AST= aspartate aminotransferase; Lab. = Laboratory; ULN = upper limit of normal. All ALT/AST values are in U/Liter; § = ALT/AST normal at baseline but increased in value on treatment.

No additional (follow-up) laboratory values were obtained for Patient 104360 despite the opportunities to do so up until visit 9 (Day 84).

**ALT/AST during visits - Study 007**

| **Table S22b** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient ID number** | **Liver Enzyme** | **Normal Range** | **Screening Day -14** | **Visit 2 Day 0** | **Visit 3 Day 14** | **Visit 4 Day 28** | **Visit 5 Day 42** | | **Dose received** |
| | | | | | | | | | |
| **506292 §** | **ALT** | **0 - 30** | **52** | | | **299** | | | **Placebo TID** |
| | **AST** | **0 - 30** | **64** | | | **222** | | | |
| | | | | | | | | | |
| **161458** | **ALT** | **6 - 43** | **236** | | | **59** | **54** | | **75mg AI TID** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **AST** | **10 - 40** | **104** | | | **33** | **34** | | |
| | | | | | | | | | |
| ID = identification; ALT = alanine aminotransferase; **AST=** aspartate aminotransferase; Lab. = Laboratory.<br>All ALT/AST values are in U/Liter; **§** = ALT/AST normal at baseline but increased in value on treatment. | | | | | | | | | |

***MO Comments:*** *Among study 005 patients with ALT/AST elevation > 5x ULN (table S22a), patient 401138 had ALT/AST elevation > 5x ULN at screening although normalized at baseline. However, patient 104360 had ALT elevation > 2x ULN with elevation to > 3x ULN by Day 42; AST rose from normal value at baseline to > 5x ULN at Day 42 (visit 6). No additional (follow-up) values were obtained despite the opportunities to do so up until visit 9 (Day 84) to ascertain time to resolution of the problem. Similarly, in study 007, patient 506292 (table S22b) also had only slightly elevated ALT and AST values at screening; both enzyme values rose to > 5x ULN at Day 28 (visit 4). There were no values obtained at Day 42. The two exculpatory points for AI in this instance are that:*

1. *evidence of enzyme value elevation was already present at screening and (in the case of patient 401138) at baseline, even before each patient received the first dose of AI*
2. *patient 506292 received placebo treatment and had greater elevation at Day 28.*

**Number (%) of patients with Chemistry Laboratory abnormalities in Studies 005 and 007**

| **Table S23:** | **№ (%) of patients with chemistry lab. abnormalities in Studies 005 and 007** | | | |
|---|---|---|---|---|
| | **Phase 3 Double –Blind Studies** | | | |
| | **Pooled Study 007 & Study 005 (TID arms Only)** | | **Study 005 (BID Arms Only** | |
| **AEs (Preferred term)** | 75 mg TID | Placebo TID | N = 69 | Placebo BID |
| ⇓ | N = 146 | N = 122 | 75 mg BID | N = 38 |
| **ALT** | | | | |
| >5x-10x ULN | - | 1 (0.8) | - | - |
| >3x-5x ULN - ↑ from normal BL | - | | 1 (1.4) | - |
| | | | | |
| **AST** | | | | |
| >10x ULN – 20 x ULN | - | - | | - |
| >5x-10x ULN | - | 1 (0.8) | 1 (1.4) | - |
| >3x-5x ULN - ↑ from normal BL | - | - | - | - |
| | | | | |
| **Bili (> 1.5 x ULN)** | | | | |
| Rise from normal baseline levels | - | - | 1 (1.4) | - |
| Rise from abnormal baseline levels | - | - | - | - |
| | | | | |
| **Clinically significant GGT ↑** | | - | | - |
| >5x-10x ULN | - | 2 (1.6) | 1 (1.4) | - |
| >3x-5x ULN - ↑ from normal BL | - | 2 (1.6) | 3 (4.3) | - |
| | | | | |
| **Hy's Law** | - | - | - | - |
| | | | | |
| **Blood Urea Nitrogen (BUN)** | | | | |
| Increase from normal baseline | 2 (1.4) | - | 1 (1.4) | - |
| | | | | |
| **Creatinine** | | - | | |
| Rise from normal or elevated BL level | 2 (1.4) | 3 (2.5) | - | - |
| | | | | |
| **Hyperglycemia** | | | | |
| ↑ from normal baseline to < 3x ULN | 32 (21.9) | 22 (18.0) | 12 (17.4) | 10 (26.3) |
| >3x-5x ULN - ↑ from normal BL | 3 (2.1) | 3 (2.5) | - | - |
| | | | | |
| **Hypoglycemia** | | | | |
| Serum glucose ≥ 40 but < 50 (mg/dL) | 3 (2.1) | 3 (2.5) | 2 (2.9) | - |
| Serum glucose < 40 (mg/dL) | 1 (0.7) | - | - | 1 (2.6) |
| BL = Baseline; ↑ = increase; **ULN** = Upper limit of normal; U = units of glucose level = mg/dL; № = number; lab. = laboratory; - = None present or no value provided; Bili = Bilirubin | | | | |

***MO Comments:*** *Regarding study 005 and 007 patients analyzed in Table 23, the rates of hyper- and hypo-glycemia for the TID arms were comparable. For the patients who received the BID*

*regimen, the reporting rate of hyperglycemia was higher in the placebo arm. All other events in the table were either comparable or unremarkable. And, there were no Hy's law cases.*

**Number (%) of Patients with Chemistry Laboratory Abnormalities in Studies 003**

| **Table S24:** | **№ (%) of patients with chemistry lab. abnormalities in Study 003** | | |
|---|---|---|---|
| | **Phase 2 Double –Blind Study** | | |
| | 225 mg BID | 75 mg BID | Placebo BID |
| ⇓ | N = 37 | N = 37 | N = 31 |
| **ALT** | | | |
| ↑ from normal BL >3x - 5x ULN | - | - | - |
| | | | |
| **AST** | | | |
| ↑ from normal BL >3x - 5x ULN | - | - | - |
| | | | |
| **Bili (> 1.5 x ULN)** | | | |
| Rise from normal baseline levels | - | - | 1 (3.2) |
| | | | |
| **Clinically significant GGT ↑** | | | |
| >3x-5x ULN - ↑ from normal BL | - | - | - |
| | | | |
| **Blood Urea Nitrogen (BUN)** | | | |
| Increase from normal baseline | 3 (8.1) | 1 (2.7) | - |
| | | | |
| **Creatinine** | | | |
| Rise from normal or elevated BL level | 1 (2.7) | - | 1 (3.2) |
| | | | |
| **Hyperglycemia (> 115 mg/dL)** | | | |
| ↑ but to < 3x ULN from normal baseline | 7 (18.9) | 8 (21.6) | 5 (16.1) |
| >3x-5x ULN - ↑ from normal BL | - | 1 (2.7) | - |
| | | | |
| **Hypoglycemia** | | | |
| Serum glucose ≥ 40 but < 50 (mg/dL) | - | 1 (2.7) | 1 (3.2) |
| Serum glucose < 40 | - | - | - |
| BL = Baseline; ↑ = increase; **ULN** = Upper limit of normal; U = units of glucose level = mg/dL; № = number; lab. = laboratory; - = None present or no value provided; Bili = Bilirubin. | | | |

***MO Comments:*** *There were more cases of hyperglycemia than any other chemistry lab abnormalities among study 003 patients. Those who received the 75 mg BID dose had a higher rate [total = 9 (24.3%)] of hyperglycemia (with normal serum glucose at baseline) compared to* 7 (18.9%) *who received 225 mg BID, or* 5 (16.1%) *who received placebo. The way these rates compare to one another show no apparent consistency to the experiences of patients in studies 007 and 005. There is no discernable dose-related derangement of glucose homeostasis associated with the receipt of AI.*

## Number (%) of patients with chemistry abnormalities in Study 006

| **Table S25a** | **Number (%) of patients with chemistry abnormalities in Study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg TID N = 125** | **75 mg BID N = 82** |
| **ALT** | | |
| ↑ from normal BL <3x | 23 (18.4) | 19 (23.2) |
| ↑ from normal BL >3x - 5x ULN | 1 (0.8) | - |
| ↑ from normal BL >5x – 10x ULN | - | 1 (1.2) |
| ↑ from normal BL >10x - 20x ULN | 1 (0.8) | - |
| | | |
| **AST** | | |
| ↑ from normal BL <3x | 16 (12.8) | 11 (13.4) |
| ↑ from normal BL >3x - 5x ULN | | |
| ↑ from normal BL >5x – 10x ULN | 1 (0.8) | - |
| ↑ from normal BL >10x - 20x ULN | 1 (0.8) | - |
| | | |
| **Total Bili** | | |
| Rise from normal baseline levels to > 1.5 x ULN | 1 (0.8) | - |
| Rise from normal baseline levels to < 1.5 x ULN | 5 (4.0) | 7 (8.5) |
| | | |
| **Clinically significant GGT ↑** | | |
| ↑ from Baseline | 22 (17.6) | 21 (25.6) |
| | | |
| **Hy's Law** | - | - |
| | | |
| **Blood Urea Nitrogen (BUN)** | | |
| Increase from normal baseline | 8 (6.4) | 8 (9.8) |
| | | |
| **Creatinine** | | |
| Rise from normal or elevated BL level | 13 (10.4) | 10 (12.2) |
| | | |
| **Hyperglycemia** | | |
| ↑ but < 3x ULN from normal baseline | 51 (40.8) | 38 (46.3) |
| >3x-5x ULN - ↑ from normal BL | 3 (2.4) | 3 (3.7) |
| | | |
| **Hypoglycemia** | | |
| **Serum glucose ≥ 40 but < 50 (mg/dL)** | 5 (4.0) | 4 (4.9) |
| **Serum glucose < 40** | 1 (0.8) | - |
| | | |

BL = Baseline; ↑ = increase; **ULN** = Upper limit of normal; U = units of glucose level = mg/dL; № = number; lab. = laboratory; Bili = Bilirubin; - = None present or no value provided.

***MO Comments:*** *Regimen-related chemistry abnormalities are not apparent among study 006 patients as shown in table S25a above. Most cases of ALT/AST elevation were less than 3 times ULN. There was an outlier (see table S25b) who had ALT and AST levels of 10x – 20x ULN. At screening and on Days 0, 28, 42, 56 and 84, ALT and AST values were normal. On Day 112,*

*ALT was 437 and AST was 405 (both in U/L). The tests were not repeated for verifification and to rule out a possible lab error or a possible mix-up with another patient's specimen or mistaken specimen labeling. Otherwise, the ALT and AST values were normal before and after visit 8 (Day 112). The Sponsor appeared to have offered no explanation for the enzyme elevations. No patient had bilirubin level > 2x ULN. No case met Hy's law.*

*There were many cases of hyperglycemia as shown in the table. Some had high glucose levels at baseline. Hyperglycemia is an expected finding, since diabetes is a common consequence of cystic fibrosis. One case had serum glucose < 40 mg/dL. Relationship to the receipt of AI could not be determined, given the many concomitant medications the patient was receiving (or had received).*

**ALT/AST Profile for Patient 147290 who received 75 mg AI TID**

| **Table S25a** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient ID number** | **Liver Enzyme** | **Normal Range For Lab.** | **Screening Day - 14** | **Visit 2 Day 0** | **Visit 3 Day 28** | **Visit 5 Day 56** | **Visit 7 Day 84** | **Visit 8 Day 112** | **Visit 9 Day 140** |
| **147290** | | | | | | | | | |
| **Dose = 75 mg of AI TID** | **ALT** | **6 - 43** | **13** | **18** | **15** | **16** | **19** | **437** | **19** |
| | **AST** | **11 - 36** | **17** | **19** | **16** | **16** | **20** | **405** | **19** |
| | | | | | | | | | |
| ID = identification; ALT = alanine aminotransferase; **AST=** aspartate aminotransferase; Lab. = Laboratory; ULN = upper limit of normal. All ALT/AST values are in U/Liter; **§** = ALT/AST normal at baseline but increased in value on treatment. | | | | | | | | | |

## Chemistry Changes in Phase 1 Studies

The Sponsor reported that there were no notable changes from baseline observed in any clinical chemistry parameters. No clinical chemistry value was reported as an AE. One adult patient's ALT/AST values increased from baseline values of 28/29 U/L to Visit 5 values of 154/278 U/L. The patient (013-2) reported heavy alcohol consumption the night before Visit 5. One microscopy result from one subject (190 mg inhaled aztreonam) was reported as an adverse event, but this was not considered to be related to treatment with study drug.

### *7.4.3 Vital Signs*

Vital signs measured included pulse/heart rate, systolic/diastolic blood pressures (BPs), respiratory rate and body temperature (oral and axillary). These were measured at all scheduled visits. Abnormal vital signs are for the comparative studies 007 and 005 are shown in table S26 and for study 003 in table S27. Study 006 patients are reported in table S28. Values were compared between AI-treated and placebo-treated patients within the comparative studies. The left side of each table shows the vital signs analyzed and the parameters used for their analysis.

**Blood Pressure**

**Systolic BP:** 19/146 (13.0 %) patients who received AI TID developed post baseline increase in systolic BP (>140 mmHg) compared to 19/122 (15.6) patients who received placebo TID. These rates were comparable. There was one case with low systolic BP in a patient who received AI TID. Patients who received placebo BID had a higher rate (21.1%) of systolic BP elevation than patients who received AI BID (13.0%). Hypertension was not reported as TEAE for any patient.

**Diastolic blood:** The diastolic BP elevation rates in both TID and BID were comparable. Patients with diastolic BP < 40 seemed to have occurred in sicker patients and were reported in 3/146 (2.1%) patients in the AI TID arm while one occurred in the placebo BID arm. Hypotension was reported as a TEAE for one of the patient (40452) who received AI TID treatment. This TEAE was considered moderate in severity and unlikely to be related to the trial drug.

**Pulse/ Heart Rate**

The rates of tachycardia were low and comparable across all study arms although tachycardia was not reported in the AI BID arm of study 005, as shown in table S26. Some patients had TEAEs relating to heart rate-related abnormalities during the AI/placebo period. Four (2.7%) patients who received AI TID had tachycardia compared to one (0.8%) who received placebo TID. One patient (placebo BID) had a TEAE of supraventricular extrasystoles considered unlikely to be related to the trial drug.

Some patients had low pulse/heart rate < 60 beats/minute but the placebo rate in either BID or TID regimen arm was higher than the corresponding AI arm.

**Temperature**

As shown in table S26, 6/146 (4.1%) who received AI TID reported temperature ≥ $100.4^{0}$ F ($38^{0}$C) versus none in the placebo arm. In the BID arm of the studies, the rates are small and comparable. Many had low temperature although at fairly comparable rates with the placebo arms in the two regimen groups.

TEAE of fever was reported at slightly higher rates in AI-treated patients than in the placebo groups. Thus, in 19/146 (13.0%) patients who received AI TID reported fever compared to 10/122 (8.2%) who received placebo TID. Similarly, 9/69 (13.0%) patients who received AI BID reported fever compared to 2/38 (5.3%) who received placebo TID. More TEAEs of pyrexia were reported at higher frequencies than the number of patients who reported temperatures ≥$38^{0}$C ($100.4^{0}$ F), the traditional level at or beyond which is considered clinical fever.

**Respiratory Rate**

Higher respiratory rate (approximately 20 respirations/ minute) values are consistent with a diagnosis of moderate to severe CF and the patient population in this trial. As shown in table S26, the respiratory rates seen in AI-treated patients were slightly higher than the rates in placebo-treated patients.

## Number (%) of patients with vital sign abnormalities in Studies 005 and 007

| Table S26: | Number (%) of patients with vital sign abnormalities in Studies 005 and 007 | | | |
|---|---|---|---|---|
| | | | | |
| | Pooled Study 007 & Study 005 (TID arms Only) | | Study 005 (BID Arms Only) | |
| Vital Sign Parameters Evaluated | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| **Systolic BP** | | | | |
| Systolic BP >140 mm Hg | 19 (13.0) | 19 (15.6) | 9 (13.0) | 8 (21.1) |
| Systolic BP < 70 mm Hg | 1 (0.7) | - | - | - |
| | | | | |
| **Diastolic BP** | | | | |
| Diastolic BP >95 | 3 (2.1) | 3 (2.5) | 2 (2.9) | 1 (2.6) |
| Diastolic BP < 40 | 3 (2.1) | - | - | 1 (2.6) |
| | | | | |
| **Pulse Rate** | | | | |
| Heart Rate >120 beats/min | 4 (2.7) | 3 (2.5) | - | 1 (2.6) |
| Heart Rate < 60 beats/min | 6 (4.1) | 14 (11.5) | 4 (5.8) | 3 (7.9) |
| | | | | |
| **Respiratory Rate** | | | | |
| Respiratory Rate > 30 | 11 (7.5) | 4 (3.3) | 5 (7.2) | 2 (5.3) |
| Respiratory Rate < 10 | - | - | - | 1 (2.6) |
| | | | | |
| **Temperature** | | | | |
| Axillary/ Oral Temp ≥ 100.4 $^0$F (38$^0$C) | 6 (4.1) | - | 1 (1.4) | 2 (5.3) |
| Axillary/ Oral Temp ≤ 95.9 $^0$F (35.5$^0$C) | 15 (10.3) | 12 (9.8) | 11 (15.9) | 4 (10.5) - |
| Fever Reported as AE | 19 (13.0) | 10 (8.2) | 9 (13.0) | 2 (5.3) |
| | | | | |
| BP = Blood Pressure; ↓ = Decrease; ↑ = Increase ; - = No parameter value recorded for the patient; Temp = Temperature; F = Fahrenheit | | | | |

***MO Comments:*** *In the temperature segment of table S 26, the two features that emerge comprise: 1.) The incidence of fever in the AI TID-treated patients compared to none in placebo TID-treated patients and 2. ) the differences in the numbers of patients to whom the Sponsor assigned the AE of pyrexia compared to the study patients who had true fever, with a temperature* ≥ 100.4 $^0$F (38$^0$C). *The Sponsor/investigators may have used a lower threshold or cut-off temperture figure at or beyond which the AE of pyrexia was assigned. Although it may have been due to subjective reports of fever or part of CF disease exacerbation despite the imbalance with placebo arm. Aztreonam in systemic use is not known to be a thermogenic agent.*

**Number (%) of patients with vital sign abnormalities in Study 003**

| **Table S27:** | **Vital sign abnormalities in Study 003 Patients** | | |
|---|---|---|---|
| | **Phase 2 Double –Blind Study** | | |
| **AEs (Preferred term)** ⇓ | 225 mg BID N = 37 | 75 mg BID N = 37 | Placebo BID N = 31 |
| **Systolic BP** | | | |
| Systolic BP >140 mm Hg | 3 (8.1) | 3 (8.1) | 6 (19.4) |
| Systolic BP < 70 mm Hg | - | - | - |
| **Diastolic BP** | | | |
| Diastolic BP >95 | 1 (2.7) | - | 1 (3.2) |
| Diastolic BP < 40 | - | 1 (2.7) | - |
| **Pulse Rate** | | | |
| Heart Rate >120 beats/min | - | 1 (2.7) | - |
| Heart Rate < 60 beats/min | 5 (13.5) | 4 (10.8) | 1 (3.2) |
| **Respiratory Rate** | | | |
| Respiratory Rate > 30 | 1 (2.7) | - | 1 (3.2) |
| Respiratory Rate < 10 | - | - | - |
| **Temperature** | | | |
| Axillary/ Oral Temp ≥ 100.4 $^0$F (38$^0$C) | 1 (2.7) | 1 (2.7) | - |
| Axillary/ Oral Temp ≤ 95.9 $^0$F (35.5$^0$C) | 7 (18.9) | 6 (16.2) | 5 (16.1) |
| Fever Reported as AE | 5 (13.5) | 3 (8.1) | 2 (6.5) |

***MO Comments:*** *The following may be said about study 003, based on table S27:*

1. *That there is a higher frequency of high systolic (BP >140 mm Hg) in the placebo arm than in the AI arms of the study. The reason is unclear. The figures are small.*
2. *As in studies 007 and 005, the numbers of patients in study 003 to whom the Sponsor assigned the AE of pyrexia were higher than the study patients who had true fever (i.e., temperature* ≥ 100.4 $^0$F (38$^0$C), *as was the case in studies 007 and 005. The possible explanations were provided under S26.*
3. *The incidence of low heart rates in patients who received AI (225 mg or 75 mg BID) was higher than in patients who received placebo.*
4. *The incidence of the other vital sign changes was either low or comparable across study arms.*

**Number (%) of patients with vital sign abnormalities in Study 006**

| Table S28 Number (%) of patients with vital sign abnormalities in Study 006 | | |
|---|---|---|
| Vital Sign Parameters Evaluated | 75 mg TID N = 125 | 75 mg BID N = 82 |
| ⇓ | | |
| **Systolic BP** | | |
| Systolic BP >140 mm Hg | 21 (16.8) | 15 (18.3) |
| Systolic BP <70 mm Hg | - | - |
| | | |
| **Diastolic BP** | | |
| Diastolic BP >95 | 2 (1.6) | 3 (3.7) |
| Diastolic BP < 40 | - | 1 (1.2) |
| | | |
| **Pulse Rate** | | |
| Heart Rate >120 beats/min | 7 (5.6) | 6 (7.3) |
| Heart Rate < 60 beats/min | 9 (7.2) | 2 (2.4) |
| | | |
| **Respiratory Rate** | | |
| Respiratory Rate > 30 | 8 (6.4) | 4 (4.9) |
| Respiratory Rate < 10 | - | - |
| | | |
| **Temperature** | | |
| Axillary/ Oral Temp ≥ 100.4 $^0$F (38$^0$C) | 2 (1.6) | 2 (2.4) |
| Axillary/ Oral Temp ≤ 95.9 $^0$ F (35.5$^0$C) | 10 (8.0) | 5 (6.1) |
| Fever Reported as AE | 37 (29.6) | 29 (35.4) |
| | | |

***MO Comments:*** *Aside from the incidence of low pulse rate which is slightly higher in the TID arm compared to the BID arm, all other frequency rates are similar and no regimen effect is apparent.*

## Vital Sign Changes in Phase 1 Studies

The Sponsor reported that there were no notable mean changes from baseline in systolic and diastolic pressure, pulse rate, oral temperature, respiration rate or pulse oximetry in subjects dosed with placebo or AI in Phase 1 studies. No individual subject value in any of the vital signs parameters was reported as an AE.

### *7.4.4 Electrocardiograms (ECGs)*

There were no ECGs performed in the Phase 2 and Phase 3 studies by the Sponsor for this NDA. In Phase 1 studies, however, the Sponsor reported that there were no notable mean changes from baseline in any ECG parameter assessed and in Phase 1 subjects and patients following the receipt of AI. In addition, they further reported that no individual subject ECG value was

reported as an AE. And "No changes from baseline were noted on any post dose physical examination."

### *7.4.5 Special Safety Studies*

Not applicable.

### *7.4.6 Immunogenicity*

No immunogenicity study was conducted for this NDA.

## 7.5 Other Safety Explorations

### *7.5.1 Dose Dependency for Adverse Events*

Dose dependency for AEs is not apparent from the data submitted for this NDA. In study 003, the Sponsor's Phase 2 study, 225 mg and 75 mg doses were expored for 14 days duration in CF patients. This informed the Sponsor's selection of 75 mg TID as their to-be-marketed dose. The choice of that dose over a higher dose supposedly resulted from association of a higher dose with more treatment-related pulmonary AEs.

### *7.5.2 Time Dependency for Adverse Events*

Duration dependence for AEs in this NDA could be ascertained by comparing AEs in study 003 where BID regimen was used in all three arms for 14 days to the BID arm in study 005 where a similar regimen was used for 28 days. Both of the studies are double-blind placebo controlled studies. Although the rates would be the parameters to be compared, it is however noteworthy that the AI BID arm in study 005 has a denominator about twice that of the AI BID arm of study 003. That notwithstanding, it appears that the longer the duration of use, the greater the number of AEs reported, although they may occur in a frequency that may have no proportional or linear relationship with time. On the other hand, although study 006 is an open-label study, where patients were exposed to multiple cycles of AI, the AE rates are generally higher than the rates seen in studies 007 and 005. Despite the different designs of the studies, that study 006 patients had extended exposure in multiple cycles of AI (compared studies 005 and 007 patients who had exposure to one cycle), one should expect higher rates of AEs. That did happen. How much higher rates in general terms should be expected with increasing number of cycles? There are no set expectations and therefore the question is purely academic at this time.

### *7.5.3 Drug-Demographic Interactions*

Safety-wise, drug-demographic interactions in this review were apparent in the following demographic groups:

**Age:** The pediatric patients tended to repond better to treatment than the older CF patients whose lungs had suffered more insults and more excerbations in life. Older CF patients suffered more treatment failures. Treatment failure is an AE.
Moreover, Pediatric CF patients in the study tended to have higher frequency of cough in response to inhalational treatment than adult CF patients. For example, per the Sponsor's analysis, cough was observed in 59% of pediatric patients vs 49% of adults; and pyrexia was observed in 18% of pediatric patients vs 9% of adults.

**Gender:** In the overall evaluation by system organ class (SOC) in studies 007,005 and 003, females were more likely to have AEs than males if they received AI. In respiratory, thoracic and mediastinal disorders (70% males vs 86% females); and gastrointestinal disorders (17% males vs 31% females); in general disorders and administration site conditions (19% males vs 30% females), the gender differences in rates are apparent. Whereas, gender differences for these SOCs were less pronounced in patients who received placebo - respiratory, thoracic and mediastinal disorders (73% males vs 74% females); gastrointestinal disorders (14% males vs 18% females).
For selected individual AEs: notable differences for AI-treated patients included cough (46% males vs 59% females), dyspnea (6% males vs 13% females), hemoptysis (6% males vs 11% females), pyrexia (9% males vs 14% females), and wheezing (10% males vs 18% females). Within gender comparison, chest discomfort was similar between treatment groups for male and female AI-treated patients (9% AI vs 8% placebo); the incidence of hemoptysis was similar between treatment groups for female patients (11% AI vs12% placebo).

**Race/Ethnicity:** There were not sufficient numbers of African American or Hispanic patients in the submission to draw conclusions about differences in AEs. In studies 005 and 007, there were 3 African Americans and 12 Hispanic patients who received AI treatment. This is expected, given that CF is a genetic disease, seen mainly in Caucasian persons.

### *7.5.4 Drug-Disease Interactions*

**Baseline Disease Severity:** Per the Sponsor, among patients treated with AI (in studies 007, 005 and 003), the incidence of respiratory symptoms and other AEs was lower in the subgroup of patients with baseline FEV1 % predicted > 50% (consistent with the relatively better lung function in these patients) than in patients with FEV1 % predicted ≤ 50%, even after controlling for age.

### *7.5.5 Drug-Drug Interactions*

According to the proposed product label, and as reported in the Clinical Pharmacology review, "No formal clinical studies of drug interactions with CAYSTON have been conducted. (b) (4)

(b) (4)

Drug-disease interaction information for AI is not available.

## 7.6 Additional Safety Explorations

Aside from some literature review, no other safety explorations were done for this NDA review.

### *7.6.1 Human Carcinogenicity*

This has been reviewed by Dr. Amy Ellis. Acccording to the Sponsor, a preclinical 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 maximum recommended human dose (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 females at 120 mg/kg/day. There was no such effect at 56 or 31 mg/kg/day.
In addition, as described in the labeling for Azactam® (aztreonam for injection) "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".

### *7.6.2 Human Reproduction and Pregnancy Data*

No reproductive toxicology study data were submitted by the Sponsor; no such study has been done with AI. As described in the labeling for Azactam (aztreonam for injection), aztreonam has been shown to cross the placenta into fetal circulation. No evidence of embryopathy or teratogenicity has been demonstrated in pregnant animals (rats and rabbits) treated with daily doses of aztreonam for injection in the order up to 15 times (in rats) and 5 times (in rabbits) recommended human dose. In the late gestation, and during lactation, no drug-induced changes in maternal, fetal or neonatal changes were observable. No adequate and well-controlled human studies of aztreonam for injection have been conducted in pregnant women.

### *7.6.3 Pediatrics and Effect on Growth*

Pediatric CF patients 6 years and older were included in the studies submitted by the Sponsor for this NDA. In the 2 Phase 3 pivotal studies submitted for NDA 50814, 83/375 (22.1%) were pediatric patients age 17 years and under. Of these, 55/375 (14.7) received AI. In the clinical studies no dose adjustments were made for pediatric patients. Pyrexia was more commonly reported in pediatric than adult patients in the placebo-controlled studies.

### *7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound*

According to the proposed product label, "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."

## 7.7 Additional Submissions

Not Applicable

# 8 Postmarketing Experience

No post-marketing experience is known with AI at this time as it is a new formulation of an old product and is the only aztreonam inhalational product studied so far. However, the post marketing information on aztreonam for injection is described under section 2.4 of this review.

# 9 Appendices

## 9.1 Literature Review

The Sponsor submitted 54 literature references for review as part of the 505 (b)(2) application for the review of AI. The literature references were submitted to provide additional safety information to supplement safety data generated from the studies conducted by the Sponsor. In their exclusivity request, the Sponsor referenced the following two additional articles which reported studies performed with inhaled aztreonam apparently outside of the Sponsor's aztreonam development program:

> 1. Fernández JD, Santiago RT, Matacon MP, Mayo RC, Sánchez GT. Inhaled Aztreonam therapy in patients with cystic fibrosis colonized with "Pseudomonas aeruginosa". Anales Espanoles de Pediatria (Spanish Annals on Pediatrics) 1994; 40(3).
>
> 2. Woo MS, Horn MV, Mason W, Ross L, Starnes VA. Use of aerosolized aztreonam in CF lung transplant patients colonized with Burkholderia cepacia (419). Pediatric Pulmonology 2002; S24:322.

The reviewer tried to select from the list of articles provided by the Sponsor that might be relevant to the review. The various articles focused on different aspects of CF disease, including the challenges involved in the management of the disease; the patients, their quality of life, etc. Some examples of articles sent include:

Abbott J and Gee L: the quality of lives of CF (particulrly pediatric) patients and management of

the disease and implications for trial design;

Aires JR, Kohler T, et al: Mechanism of resistance of *Pseudomonas aeruginosa* to aminoglycosides

Andrews R, Fasoli R, et al: discussed use of combined intravenous aztreonam/gentamicin for the treatment of lower respiratory tract infection involving *Pseudomonas aeruginosa* infection

Burn J, Emerson J, et al: Microbiology of Sputum from patients at CF centers in the U.S.

Gibson RL, Retsch-Bogart GZ et al: Microbiology, safety PK of Aztreonam Lysinate for Inhalation in patients with CF;

Valerius NH, Koch C, et al: Prevention of Chronic *Pseudomonas aeruginosa* colonization in CF by early treatment

Yankaskas JR et al: CF Adult care Concensus conference report

***MO comments:*** *I found the paper by Gibson RL, Retsch-Bogart GZ et al the most relevant of the articles. It was a double-blind, placebo-controlled, dose escalation trial to determine PK and tolerability of AI in patients with CF. They explored three AI doses (75 mg, 150 mg and 225 mg) in addition to a placebo cohort, and found no dose-reated AE. It was the one paper that specifically addressed the use of AI and also elicited safety information.*
*The study corroborated our review findings. As in the NDA review, increased cough was the most common AE. They also found no dose-relationship to the development of AEs.*

**Post script:** ***The article discussed above*** *turned out to be a study done with or for Corus Pharma in Seattle, Washington. The data eventually became Gilead's study 002 which the MO has already reviewed.*

## Literature References

1. Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med.* 2003 Oct 15;168(8):918-51. Review.

2. Manno G, Cruciani M, Romano L, Scapolan S, Mentasti M, Lorini R, Minicucci L. Antimicrobial use and Pseudomonas aeruginosa susceptibility profile in a cystic fibrosis centre. *Int J Antimicrob Agents.* 2005 Mar;25(3):193-7.

3. Ennis DM, Cobbs CG. The newer cephalosporins, aztreonam and imipenem. *Infect Dis Clin North Am* 1995; 9; 687.

4. Shawar RM, MacLeod DL, Garber RL, Burns JL, Stapp JR, Clausen CR, Tanaka SK.

Aminoglycoside-resistance mechanisms for cystic fibrosis Pseudomonas aeruginosa isolates are unchanged by long-term, intermittent, inhaled tobramycin treatment.
*J Infect Dis*. 2000 Mar;181(3):1180

## 9.2 Labeling Recommendations

No labeling recommendation is being made at this time. After completing NDA # 50814 review, the reviewer has found the clinical evidence provided by one of the two pivotal studies (study 007) adequate to establish the efficacy of AI for use in the treatment and improvement of respiratory signs and symptoms and lung functions in CF patients with chronic *Pseudomonas aeruginosa* infection. However, the reviewer does not accept the results of study 005 as adequate evidence to support study 007 data. Therefore, another study is recommended to provide adequate evidence to support study 007 data for possible approval of AI.

## 9.3 Advisory Committee Meeting

No advisory committee was held for this application.

## Appendix 1

## Common TEAEs in Studies 005 and 007

| Table S11b: | Number (%) of TEAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double–Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID Arms Only) | | Study 005 (BID Arms Only) | |
| TEAEs (Preferred term) | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Abdominal discomfort | - | - | - | 2 (5.3) |
| Abdominal distension | - | - | 2 (2.9) | - |
| Abnormal chest sound | 4 (2.7) | 1 (0.8) | - | 1 (2.6) |
| Acne | - | 1 (0.8) | 1 (1.4) | - |
| ↑ ALT | - | 1 (0.8) | 3 (4.3) | - |
| Anorexia | 2 (1.4) | 1 (0.8) | - | 1 (2.6) |
| Anxiety | 3 (2.1) | - | 1 (1.4) | - |
| Arthralgia | 1 (0.7) | 6 (4.9) | 3 (4.3) | 1 (2.6) |
| Arthropod bite | - | - | 1 (1.4) | - |
| ↑ AST | - | - | 3 (4.3) | - |
| Asthma | 2 (1.4) | - | - | - |
| Asthenia | 2 (1.4) | 3 (2.5) | 1 (1.4) | 1 (2.6) |
| Autoimmune thyroiditis | 1 (0.7) | - | - | - |
| Back pain | 1 (0.7) | 4 (3.3) | - | - |
| Band neutrophil count increased | 1 (0.7) | - | - | - |
| Blood glucose decreased | - | 2 (1.6) | 1 (1.4) | - |
| Blood glucose increased | 6 (4.1) | 2 (1.6) | 1 (1.4) | 2 (5.3) |
| Blood potassium increased | 1 (0.7) | - | - | - |
| Blood urine present | 1 (0.7) | - | - | - |
| Bone pain | - | 1 (0.8) | - | - |
| Breast swelling/ mass | 2 (1.4) | - | - | - |
| Breath sounds decreased | 5 (3.4) | 4 (3.3) | - | - |
| Bronchiectasis | 1 (0.7) | - | - | - |
| Bronchitis acute | - | 1 (0.8) | - | 1 (2.6) |
| Candidiasis NOS | - | 1 (0.8) | - | - |
| Central venous catheterisation | - | - | 1 (1.4) | - |
| Chest pain | 2 (1.4) | 2 (1.6) | 1 (1.4) | 1 (2.6) |
| Chills | 4 (2.7) | 4 (3.3) | 1 (1.4) | - |
| Clavicle fracture | - | - | 1 (1.4) | - |
| Conjunctivitis | 2 (1.4) | - | 1 (1.4) | - |
| Constipation | 2 (1.4) | 1 (0.8) | - | 1 (2.6) |
| Contusion | 2 (1.4) | 1 (0.8) | - | - |
| Cyst | - | 1 (0.8) | - | - |
| → = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified<br>↑ ALT = Alanine aminotransferase increased; ↑ AST = Aspartate aminotransferase increased | | | | |

## Common TEAEs in Studies 005 and 007 - (Continued)

| Table S11c: | Number (%) of TEAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double–Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID Arms Only) | | Study 005 (BID Arms Only) | |
| TEAEs (Preferred term) | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Decreased activity | 1 (0.7) | - | - | - |
| Dehydration | 1 (0.7) | - | - | - |
| Depression | 1 (0.7) | - | - | - |
| Diabetes mellitus (poor control) | - | 1 (0.8) | - | - |
| Dizziness | 3 (2.1) | 2 (1.6) | 2 (2.9) | - |
| Dry throat | 1 (0.7) | - | 1 (1.4) | 1 (2.6) |
| Dysgeusia | 1 (0.7) | 1 (0.8) | - | - |
| Dysmenorrhoea | - | 1 (0.8) | 1 (1.4) | - |
| Dyspepsia | 1 (0.7) | 1 (0.8) | 1 (1.4) | 1 (2.6) |
| Dysphonia | 4 (2.7) | 4 (3.3) | 1 (1.4) | 4 (10.5) |
| Dysuria | - | 1 (0.8) | - | - |
| Ear congestion | 1 (0.7) | 2 (1.6) | 1 (1.4) | - |
| Eosinophil count increased | - | - | - | 1 (2.6) |
| Epistaxis | 6 (4.1) | 2 (1.6) | 2 (2.9) | 2 (5.3) |
| Erythema | 2 (1.4) | - | 1 (1.4) | - |
| Eye discharge | 1 (0.7) | - | - | - |
| Eye pruritus | 3 (2.1) | - | - | 2 (5.3) |
| Facial pain | - | 1 (0.8) | - | - |
| Feeling hot | 1 (0.7) | - | 1 (1.4) | - |
| $FEV_1$ decreased | 3 (2.1) | 4 (3.3) | 4 (5.8) | 2 (5.3) |
| Flank pain | 4 (2.7) | 1 (0.8) | 1 (1.4) | - |
| Flatulence | 2 (1.4) | 1 (0.8) | 4 (5.8) | - |
| Frequent bowel movements | 1 (0.7) | - | - | - |
| Fracture -Ankle | - | - | - | 2 (5.3) |
| Gamma-glutamyltransferase ↑ | - | 1 (0.8) | 1 (1.4) | - |
| Gastritis | - | 1 (0.8) | - | - |
| Gastroenteritis viral | 1 (0.7) | - | - | 1 (2.6) |
| Gastrooesophageal reflux disease | 2 (1.4) | 1 (0.8) | - | - |
| Gingival pain | 1 (0.7) | - | - | - |
| Glossodynia | - | - | 1 (1.4) | - |
| Glucose tolerance impaired | - | - | 1 (1.4) | - |

→ = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified
↑ ALT = Alanine aminotransferase increased; ↑ AST = Aspartate aminotransferase increased

## Common TEAEs in Studies 005 and 007 - (Continued)

| Table S11d: | Number (%) of TEAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double–Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID Arms Only) | | Study 005 (BID Arms Only) | |
| TEAEs (Preferred term) | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Haematemesis | - | 1 (0.8) | - | - |
| Haematochezia | - | - | 1 (1.4) | - |
| Hepatic enzyme ↑ NOS | 2 (1.4) | - | 1 (1.4) | - |
| Herpes simplex | 1 (0.7) | - | 2 (2.9) | - |
| Hyperhidrosis | 2 (1.4) | 1 (0.8) | - | - |
| Hypersensitivity | 1 (0.7) | - | - | - |
| Hypoaesthesia oral | 1 (0.7) | - | - | - |
| Hypophosphataemia | - | 1 (0.8) | - | - |
| Hypotension | 1 (0.7) | - | - | - |
| Increased upper airway secretion | 1 (0.7) | - | - | - |
| Viscousity of bronchial secretion ↑ | 2 (1.4) | 1 (0.8) | - | - |
| Influenza | - | - | 1 (1.4) | 1 (2.6) |
| Injection site discomfort | 1 (0.7) | - | 1 (1.4) | - |
| Insomnia | 2 (1.4) | - | 3 (4.3) | - |
| Instillation site erythema | - | - | 2 (2.9) | - |
| Joint dislocation | 1 (0.7) | - | - | - |
| Joint stiffness | 1 (0.7) | - | - | - |
| Joint swelling | 2 (1.4) | - | - | - |
| Lacrimation increased | 2 (1.4) | - | - | - |
| Laryngospasm | - | - | 1 (1.4) | - |
| Lethargy | - | 2 (1.6) | - | - |
| Leukocytosis | 3 (2.1) | 1 (0.8) | - | 1 (2.6) |
| Lip pain | 1 (0.7) | - | - | - |
| Lower respiratory tract infection | - | - | 1 (1.4) | - |
| Lymphadenopathy | 2 (1.4) | 1 (0.8) | - | - |
| Lymphocyte count decreased | - | - | - | 1 (2.6) |
| Malaise | - | 3 (2.5) | 1 (1.4) | - |
| Middle ear effusion | 2 (1.4) | - | - | - |
| Migraine | - | 1 (0.8) | - | - |
| Monocyte count increased | - | - | - | 1 (2.6) |
| Musculoskeletal chest pain | - | 3 (2.5) | 1 (1.4) | - |
| Myalgia | 5 (3.4) | 4 (3.3) | 1 (1.4) | - |

→ = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified
↑ ALT = Alanine aminotransferase increased; ↑ AST = Aspartate aminotransferase increased

## Common TEAEs in Studies 005 and 007 - (Continued)

| Table S11e: | Number (%) of TEAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double–Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID Arms Only) | | Study 005 (BID Arms Only) | |
| TEAEs (Preferred term) | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Nasal discomfort | 1 (0.7) | - | - | - |
| Nasal dryness | - | - | 1 (1.4) | - |
| Nasal edema | 4 (2.7) | 1 (0.8) | - | - |
| Nasal mucosal disorder | 3 (2.1) | 3 (2.5) | 2 (2.9) | 1 (2.6) |
| Nasal polyps | 3 (2.1) | 3 (2.5) | 1 (1.4) | 1 (2.6) |
| Nasal turbinate abnormality | - | 1 (0.8) | - | - |
| Nasopharyngeal disorder | 1 (0.7) | - | 2 (2.9) | 1 (2.6) |
| Nasopharyngitis | 3 (2.1) | - | - | - |
| Nasal septum deviation | 1 (0.7) | - | - | - |
| Neck pain | - | 1 (0.8) | - | - |
| Nephrolithiasis | 1 (0.7) | - | 2 (2.9) | - |
| Neutrophil count increased | 3 (2.1) | - | - | 1 (2.6) |
| Night sweats | 1 (0.7) | 3 (2.5) | | |
| Oedema localized | - | 1 (0.8) | - | - |
| Oedema peripheral | 3 (2.1) | 1 (0.8) | - | - |
| Oral candidiasis | - | 2 (1.6) | 1 (1.4) | - |
| Oral pain | - | 1 (0.8) | - | - |
| Orthopnoea | - | 1 (0.8) | - | - |
| Osteoarthritis | - | 2 (1.6) | - | - |
| Otitis media acute | - | - | - | 1 (2.6) |
| Oxygen saturation decreased | - | 1 (0.8) | 1 (1.4) | - |
| Pain NOS | 5 (3.4) | 2 (1.6) | 2 (2.9) | 1 (2.6) |
| Pain - extremity | 3 (2.1) | 3 (2.5) | 3 (4.3) | - |
| Pallor | - | 1 (0.8) | - | - |
| Paranasal sinus hypersecretion | 4 (2.7) | 2 (1.6) | 2 (2.9) | 2 (5.3) |
| Paraesthesia oral | 1 (0.7) | - | - | - |
| Pharyngeal erythema | 1 (0.7) | 6 (4.9) | 1 (1.4) | - |
| Pharyngitis | - | - | 1 (1.4) | - |
| Pitting oedema | - | - | 1 (1.4) | - |
| Platelet count decreased | - | - | 1 (1.4) | - |
| Pleuritic pain | - | 1 (0.8) | - | - |
| Pollakiuria | - | 1 (0.8) | - | - |
| Polyarthritis | 1 (0.7) | - | - | - |
| → = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified ↑ ALT = Alanine aminotransferase increased; ↑ AST = Aspartate aminotransferase increased | | | | |

## Common TEAEs in Studies 005 and 007 - (Continued)

| Table S11f | Number (%) of TEAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double–Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID Arms Only) | | Study 005 (BID Arms Only) | |
| TEAEs (Preferred term) | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Proctalgia | - | - | 1 (1.4) | - |
| Prolonged expiration | - | 1 (0.8) | - | - |
| Pruritus | 1 (0.7) | - | 1 (1.4) | - |
| Pulmonary congestion | 2 (1.4) | 1 (0.8) | - | - |
| Rales | 5 (3.4) | 6 (4.9) | 1 (1.4) | 2 (5.3) |
| Rash | 5 (3.4) | - | 1 (1.4) | 1 (2.6) |
| Rash maculo-papular | - | - | 1 (1.4) | - |
| Red man syndrome | - | - | 1 (1.4) | - |
| Rhinitis | 4 (2.7) | 2 (1.6) | 1 (1.4) | 1 (2.6) |
| Rhonchi | 2 (1.4) | 2 (1.6) | 2 (2.9) | |
| Seasonal allergy | - | 1 (0.8) | - | 1 (2.6) |
| Shoulder pain | - | - | 1 (1.4) | - |
| Salivary hypersecretion | - | 1 (0.8) | - | - |
| Sinusitis acute | 1 (0.7) | 2 (1.6) | 1 (1.4) | 2 (5.3) |
| Sinusitis chronic | - | 1 (0.8) | - | - |
| Skin hyperpigmentation | - | 1 (0.8) | - | - |
| Skin infection | - | - | 1 (1.4) | - |
| Skin laceration | 1 (0.7) | - | - | 1 (2.6) |
| Skin papilloma | - | 1 (0.8) | - | - |
| Skin ulcer | - | - | 1 (1.4) | - |
| Sneezing | 3 (2.1) | 2 (1.6) | - | - |
| Soft tissue injury | 1 (0.7) | - | - | - |
| Solar urticaria | 1 (0.7) | - | - | - |
| Sputum discoloured | 3 (2.1) | 4 (3.3) | 2 (2.9) | 2 (5.3) |
| Sputum decreased | 1 (0.7) | - | - | - |
| Sputum retention | - | 1 (0.8) | - | - |
| Stomach discomfort | - | - | - | 1 (2.6) |
| Stomatitis | 2 (1.4) | - | 1 (1.4) | 1 (2.6) |
| Sunburn | 1 (0.7) | 1 (0.8) | - | - |
| Supraventricular extrasystoles | - | - | - | 1 (2.6) |
| Swelling face | - | 1 (0.8) | - | - |
| Syncope | 1 (0.7) | - | - | 1 (2.6) |
| → = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified; URI = Upper respiratory tract infection; GGT = Gamma-glutamyltransferase ; ↑ = increased; NOS = Not Otherwise Specified | | | | |

## Common TEAEs in Studies 005 and 007 - (Continued)

| Table S11g | Number (%) of TEAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double–Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID Arms Only) | | Study 005 (BID Arms Only) | |
| TEAEs (Preferred term) | 75 mg TID | Placebo TID | 75 mg BID | Placebo BID |
| ⇓ | N = 146 | N = 122 | N = 69 | N = 38 |
| Tachycardia | 4 (2.7) | 1 (0.8) | - | - |
| Tachypnoea | - | 1 (0.8) | - | - |
| Thermal burn | - | - | 1 (1.4) | - |
| Throat irritation | 6 (4.1) | 3 (2.5) | - | - |
| Tinnitus | 1 (0.7) | 1 (0.8) | 2 (2.9) | - |
| Tongue discolouration | 1 (0.7) | - | 1 (1.4) | - |
| Toothache | 1 (0.7) | 1 (0.8) | - | - |
| Tooth extraction | 1 (0.7) | - | - | - |
| Tooth injury | 1 (0.7) | - | 1 (1.4) | - |
| Tuberculin test positive | - | 1 (0.8) | - | - |
| Tympanic membrane hyperaemia | - | | 1 (1.4) | - |
| Upper respiratory tract infection | 3 (2.1) | 6 (4.9) | 2 (2.9) | - |
| Urinary Urgency | - | 1 (0.8) | - | - |
| Urticaria | - | 1 (0.8) | - | - |
| Vaccination complication | - | - | 1 (1.4) | - |
| Vaginal discharge | - | 1 (0.8) | - | - |
| Vertigo | - | - | 1 (1.4) | - |
| Vitamin A decreased | - | - | - | 1 (2.6) |
| Viral infection | 1 (0.7) | - | 1 (1.4) | - |
| Vitreous detachment | 1 (0.7) | - | - | - |
| Vitreous floaters | 1 (0.7) | - | - | - |
| Weight decreased | 3 (2.1) | 4 (3.3) | 2 (2.9) | 1 (2.6) |
| Wound complication | 1 (0.7) | - | - | - |
| Wound infection | 1 (0.7) | - | - | - |

→ = Leading to or causing; CRP = C-reactive protein : NOS = Not Otherwise Specified; URI = Upper respiratory tract infection; GGT = Gamma-glutamyltransferase ; ↑ = increased; NOS = Not Otherwise Specified

## Treatment-Related AEs [TRAEs] among Studies 005 and 007 Patients

| **Table S12b:** | **Number (%) of TRAEs Reported in Study 005 and 007 Patients** | | | |
|---|---|---|---|---|
| | **Phase 3 Double –Blind Studies** | | | |
| | **Pooled Study 007 & Study 005 (TID arms Only)** | | **Study 005 (BID Arms Only** | |
| **AEs (Preferred term)** | 75 mg TID | Placebo TID | N = 69 | Placebo BID |
| ⇓ | N = 146 | N = 122 | 75 mg BID | N = 38 |
| | | | | |
| Abdominal pain | 1 (0.7) | - | - | 1 (2.6) |
| Anorexia | - | 6 (4.9) | 1 (1.4) | 1 (2.6) |
| Asthenia | - | 1 (0.8) | - | 1 (2.6) |
| Breath sounds decreased | 1 (0.7) | - | - | - |
| Bronchitis acute | - | - | - | 1 (2.6) |
| Chest discomfort | 6 (4.1) | 2 (1.6) | 1 (1.4) | - |
| Cough | 25 (17.1) | 10 (8.2) | 12 (17.4) | 7 (18.4) |
| Crackles lung | 2 (1.4) | 2 (1.6) | 1 (1.4) | - |
| Diarrhoea | 2 (1.4) | - | - | - |
| Dizziness | 1 (0.7) | - | - | - |
| Dry mouth | - | - | - | 1 (2.6) |
| Dry throat | - | - | 1 (1.4) | - |
| Dysgeusia | 1 (0.7) | 1 (0.8) | - | - |
| Dysphonia | 3 (2.1) | 1 (0.8) | 1 (1.4) | 3 (7.9) |
| Dyspnoea (including execerbated) | 6 (4.1) | 6 (4.9) | 2 (2.9) | 3 (7.9) |
| Ear congestion | - | 4 (3.3) | - | - |
| Epistaxis | - | 1 (0.8) | - | - |
| Exercise tolerance decreased | - | 3 (2.5) | - | 1 (2.6) |
| Fatigue | - | 2 (1.6) | - | - |
| Feeling hot | - | - | 2 (2.9) | - |
| Forced expiratory volume decreased | 1 (0.7) | 1 (0.8) | - | - |
| Haemoptysis | 2 (1.4) | 1 (0.8) | - | 2 (5.3) |
| Herpes simplex | - | - | 1 (1.4) | - |
| Headache | 3 (2.1) | 1 (0.8) | - | - |
| Hepatic enzyme increased | 1 (0.7) | - | - | - |
| Hypoaesthesia oral | 1 (0.7) | - | - | - |
| Lip pain | 1 (0.7) | - | - | - |
| Musculoskeletal chest pain | - | 1 (0.8) | 1 (1.4) | - |
| Nasal congestion | 2 (1.4) | 1 (0.8) | - | - |
| Nausea | - | 1 (0.8) | - | 1 (2.6) |
| Non-cardiac chest pain | 1 (0.7) | - | 1 (1.4) | - |
| Otitis media acute | - | - | - | 1 (2.6) |

## Treatment-Related AEs [TRAEs] among Studies 005 and 007 Patients – Continued

| Table S12c: | Number (%) of TRAEs Reported in Study 005 and 007 Patients | | | |
|---|---|---|---|---|
| | Phase 3 Double –Blind Studies | | | |
| | Pooled Study 007 & Study 005 (TID arms Only) | | Study 005 (BID Arms Only | |
| AEs (Preferred term) | 75 mg TID | Placebo TID | N = 69 | Placebo BID |
| ⇓ | N = 146 | N = 122 | 75 mg BID | N = 38 |
| Paraesthesia oral | 1 (0.7) | - | - | - |
| Paranasal sinus hypersecretion | - | 1 (0.8) | 1 (1.4) | - |
| Pharyngolaryngeal pain | 4 (2.7) | 3 (2.5) | 2 (2.9) | 1 (2.6) |
| Productive cough | 4 (2.7) | 7 (5.7) | - | 4 (10.5) |
| Pulmonary function test decreased | 1 (0.7) | 2 (1.6) | 1 (1.4) | - |
| Pyrexia | - | - | - | 1 (2.6) |
| Rash | 1 (0.7) | 1 (0.8) | - | - |
| Respiratory tract congestion | 1 (0.7) | 4 (3.3) | - | 1 (2.6) |
| Rhonchi | - | - | - | 1 (2.6) |
| Salivary hypersecretion | 1 (0.7) | - | - | - |
| Sinus headache | - | - | 1 (1.4) | - |
| Sneezing | 2 (1.4) | - | - | - |
| Sputum decreased | 1 (0.7) | - | - | - |
| Sputum discoloured | 2 (1.4) | 1 (0.8) | - | - |
| Stomach discomfort | - | - | - | 1 (2.6) |
| Stomatitis | 1 (0.7) | - | - | - |
| Tachycardia | 1 (0.7) | - | - | - |
| Throat irritation | 3 (2.1) | 2 (1.6) | 1 (1.4) | - |
| Tinnitus | 1 (0.7) | - | 1 (1.4) | - |
| Tongue discolouration | 1 (0.7) | - | - | - |
| Vaginal discharge | - | 1 (0.8) | - | - |
| Vomiting | 2 (1.4) | - | - | 1 (2.6) |
| Weight decreased | - | 1 (0.8) | - | - |
| Wheezing | 4 (2.7) | 5 (4.1) | 3 (4.3) | - |

## Common TEAEs in Study 003 Patients

| Table S14b: | | | |
|---|---|---|---|
| | Phase 2 Double –Blind Study | | |
| AEs (Preferred term) ⇓ | 225 mg BID N = 37 | 75 mg BID N = 37 | Placebo BID N = 31 |
| Abdominal pain | - | 1 (2.7) | 3 (9.7) |
| Arthralgia | 2 (5.4) | - | 1 (3.2) |
| Blood glucose increased | - | 1 (2.7) | - |
| Blood uric acid increased | 1 (2.7) | - | - |
| Breath sounds decreased | 1 (2.7) | - | - |
| Central venous catheterisation | - | 1 (2.7) | - |
| Chest pain | 1 (2.7) | - | - |
| Conjunctival hyperaemia | - | 1 (2.7) | - |
| Contusion | - | - | 1 (3.2) |
| Costovertebral angle tenderness | - | 1 (2.7) | - |
| Crackles lung | - | 3 (8.1) | 3 (9.7) |
| Diarrhoea | 1 (2.7) | - | - |
| Dizziness | - | 2 (5.4) | 3 (9.7) |
| Dyspepsia | 1 (2.7) | - | - |
| Dyspnoea | 3 (8.1) | 1 (2.7) | 1 (3.2) |
| Ear pain | 1 (2.7) | - | - |
| Epistaxis | - | 1 (2.7) | 1 (3.2) |
| Excoriation | - | - | 1 (3.2) |
| Eye pruritus | 1 (2.7) | - | 1 (3.2) |
| Eyelid oedema | 1 (2.7) | - | - |
| Fatigue | 2 (5.4) | 1 (2.7) | 2 (6.5) |
| Flank pain | - | 1 (2.7) | - |
| Flatulence | - | 1 (2.7) | - |
| Gout | 1 (2.7) | - | - |
| Haemoptysis | 1 (2.7) | 1 (2.7) | 2 (6.5) |
| Hoarseness | 1 (2.7) | 2 (5.4) | 1 (3.2) |

## Common TEAEs in Study 003 Patients – Continued

| Table S14c: | Phase 2 Double –Blind Study | | |
|---|---|---|---|
| | | | |
| AEs (Preferred term) ⇓ | 225 mg BID N = 37 | 75 mg BID N = 37 | Placebo BID N = 31 |
| Hypersensitivity | 1 (2.7) | - | - |
| Hypoxia | 1 (2.7) | - | - |
| Injury | 1 (2.7) | - | - |
| Joint swelling | 2 (5.4) | - | - |
| Laryngitis | 1 (2.7) | - | - |
| Loose stool | 1 (2.7) | - | - |
| Lymph node pain | - | - | 1 (3.2) |
| Lymph node palpable | - | 1 (2.7) | - |
| Lymphadenopathy | - | 1 (2.7) | 1 (3.2) |
| Malabsorption | - | - | 1 (3.2) |
| Metrorrhagia | - | - | 1 (3.2) |
| Mucous membrane disorder | - | 1 (2.7) | - |
| Muscle cramp | - | - | 1 (3.2) |
| Muscle strain | 1 (2.7) | - | - |
| Musculoskeletal chest pain | 1 (2.7) | - | - |
| Myalgia | 2 (5.4) | - | - |
| Nasal discomfort | - | 1 (2.7) | - |
| Nasal polyps | - | - | 1 (3.2) |
| Nasopharyngitis | 1 (2.7) | - | - |
| Nausea | - | 2 (5.4) | 1 (3.2) |
| Oral candidiasis | 1 (2.7) | - | - |
| Oral mucosal discolouration | - | - | 1 (3.2) |
| Pain | - | 1 (2.7) | 1 (3.2) |
| Palpitations | - | 1 (2.7) | - |
| Paranasal sinus hypersecretion | 1 (2.7) | 1 (2.7) | - |
| Pharyngeal erythema | 3 (8.1) | 3 (8.1) | 3 (9.7) |
| Pharyngitis | - | - | 1 (3.2) |
| | | | |

**Common TEAEs in Study 003 Patients - Continued**

| **Table S14d:** | **Phase 2 Double –Blind Study** | | |
|---|---|---|---|
| | | | |
| **AEs (Preferred term)** ⇓ | **225 mg BID** N = 37 | **75 mg BID** N = 37 | **Placebo BID** N = 31 |
| Pleuritic pain | 1 (2.7) | - | 1 (3.2) |
| Pulmonary congestion | - | - | 1 (3.2) |
| Rash | - | 1 (2.7) | - |
| Respiratory tract congestion | 1 (2.7) | 3 (8.1) | - |
| Respiratory tract infection | - | 1 (2.7) | - |
| Rhinitis | - | 2 (5.4) | 2 (6.5) |
| Rhinitis seasonal | 2 (5.4) | - | - |
| Rib fracture | 1 (2.7) | - | - |
| Rigors | 1 (2.7) | - | 1 (3.2) |
| Scab | 1 (2.7) | - | - |
| Sinus headache | - | 1 (2.7) | - |
| Sinus pain | - | 1 (2.7) | - |
| Skin laceration | 2 (5.4) | - | - |
| Systemic lupus erythematosus | 1 (2.7) | - | - |
| Systemic lupus erythematosus rash | 1 (2.7) | - | - |
| Tachycardia | 1 (2.7) | - | - |
| Thermal burn | - | - | 1 (3.2) |
| Throat irritation | 1 (2.7) | - | 1 (3.2) |
| Throat tightness | - | - | 1 (3.2) |
| Tongue disorder | - | 1 (2.7) | - |
| Tooth injury | - | 1 (2.7) | - |
| Upper respiratory tract infection | 1 (2.7) | - | 1 (3.2) |
| Urticaria | - | 1 (2.7) | - |
| Vomiting | 2 (5.4) | 2 (5.4) | 2 (6.5) |
| Wheezing | 3 (8.1) | 3 (8.1) | 2 (6.5) |
| White blood cell count increased | 1 (2.7) | - | - |

## Common TEAEs Reported in Study 006 Patients

| Table S16b | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| AEs preferred term | 75 mg TID N = 125 | 75 mg BID N = 82 |
| Abdominal distension | 3 (2.4) | 5 (6.1) |
| Abdominal tenderness | 2 (1.6) | - |
| Abnormal chest sound | 2 (1.6) | 1 (1.2) |
| Abscess | - | 1 (1.2) |
| Acne | 1 (0.8) | 4 (4.9) |
| Agitation | 1 (0.8) | 1 (1.2) |
| Alanine aminotransferase increased | 1 (0.8) | 2 (2.4) |
| Anaemia | 3 (2.4) | 1 (1.2) |
| Anorexia | 1 (0.8) | 3 (3.7) |
| Anxiety | 1 (0.8) | 2 (2.4) |
| Aphonia | 1 (0.8) | - |
| Aphthous stomatitis | - | 2 (2.4) |
| Arthritis | 1 (0.8) | 1 (1.2) |
| Aspartate aminotransferase increased | - | 1 (1.2) |
| Aspergillosis | 1 (0.8) | - |
| Asthenia | 11 (8.8) | 4 (4.9) |
| Asthma | 1 (0.8) | - |
| Back injury | 1 (0.8) | - |
| Back pain | 11 (8.8) | 6 (7.3) |
| Bacteria sputum identified | 1 (0.8) | - |
| Blood amylase increased | - | 1 (1.2) |
| Blood chloride decreased | 1 (0.8) | - |
| Blood chloride increased | - | 1 (1.2) |
| Blood creatinine increased | 1 (0.8) | - |
| Blood glucose decreased | 2 (1.6) | - |
| Blood glucose increased | 7 (5.6) | 3 (3.7) |
| Blood pressure increased | - | 1 (1.2) |
| Blood sodium increased | - | 1 (1.2) |
| Blood thyroid stimulating hormone decreased | - | 1 (1.2) |
| Bloody airway discharge | - | 1 (1.2) |
| Bone pain | - | 1 (1.2) |
| Breast mass | - | 1 (1.2) |
| Breath sounds decreased | 3 (2.4) | 2 (2.4) |
| Bronchiectasis | 1 (0.8) | - |

## Common TEAEs Reported in Study 006 Patients - continued

| Table S16c | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| AEs preferred term | 75 mg TID N = 125 | 75 mg BID N = 82 |
| Bronchitis | 3 (2.4) | - |
| Bronchospasm | 2 (1.6) | 1 (1.2) |
| Candidiasis | 1 (0.8) | 3 (3.7) |
| Cardiac flutter | - | 1 (1.2) |
| Cardiac murmur | 1 (0.8) | - |
| Cartilage injury | 1 (0.8) | - |
| Cellulitis | 1 (0.8) | 1 (1.2) |
| Chapped lips | 1 (0.8) | - |
| Chest pain | 3 (2.4) | 2 (2.4) |
| Chest wall pain | 3 (2.4) | 1 (1.2) |
| Chest X-ray abnormal | 2 (1.6) | 1 (1.2) |
| Chills | 7 (5.6) | 6 (7.3) |
| Clavicle fracture | 1 (0.8) | - |
| Conjunctivitis | 2 (1.6) | - |
| Constipation | 7 (5.6) | 8 (9.8) |
| Contusion | - | 2 (2.4) |
| Deafness | 1 (0.8) | 1 (1.2) |
| Decreased activity | 1 (0.8) | - |
| Dehydration | 2 (1.6) | 1 (1.2) |
| Dental caries | 1 (0.8) | - |
| Depression | 3 (2.4) | 2 (2.4) |
| Dermatitis allergic | - | 1 (1.2) |
| Diabetes mellitus | - | 1 (1.2) |
| Dilatation atrial | - | 1 (1.2) |
| Disorientation | 1 (0.8) | - |
| Distal intestinal obstruction syndrome | - | 1 (1.2) |
| Dizziness | 7 (5.6) | 4 (4.9) |
| Drug hypersensitivity | 1 (0.8) | 1 (1.2) |

## Common AEs Reported in Study 006 Patients - continued

| Table S16d | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| **AEs preferred term** | **75 mg TID** | **75 mg BID** |
| | **N = 125** | **N = 82** |
| Dry mouth | 5 (4.0) | - |
| Dry skin | 2 (1.6) | - |
| Dry throat | 1 (0.8) | 1 (1.2) |
| Dysgeusia | 2 (1.6) | 1 (1.2) |
| Dysmenorrhoea | 1 (0.8) | 1 (1.2) |
| Dyspepsia | 3 (2.4) | 2 (2.4) |
| Dysphonia | 6 (4.8) | 1 (1.2) |
| Dystonia | 1 (0.8) | - |
| Dysuria | 3 (2.4) | - |
| Ear congestion | 2 (1.6) | 2 (2.4) |
| Ear discomfort | 1 (0.8) | - |
| Ear infection | 2 (1.6) | 1 (1.2) |
| Ear pain | 7 (5.6) | 4 (4.9) |
| Ear pruritus | 1 (0.8) | - |
| Ecchymosis | 3 (2.4) | - |
| Enuresis | 1 (0.8) | - |
| Epididymal cyst | 1 (0.8) | - |
| Epistaxis | 5 (4.0) | 4 (4.9) |
| Erectile dysfunction | - | 1 (1.2) |
| Erythema | 2 (1.6) | 1 (1.2) |
| Excoriation | 2 (1.6) | 1 (1.2) |
| Expiratory reserve volume decreased | - | 1 (1.2) |
| Eye discharge | 1 (0.8) | - |
| Eye pain | 1 (0.8) | - |
| Eye pruritus | 1 (0.8) | - |
| Eye swelling | 1 (0.8) | - |
| Feeling hot | 1 (0.8) | - |
| Feeling jittery | - | 1 (1.2) |
| Feeling of body temperature change | 1 (0.8) | - |
| Flank pain | 1 (0.8) | - |

## Common TEAEs Reported in Study 006 Patients - continued

| Table S16e | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| AEs preferred term | 75 mg TID N = 125 | 75 mg BID N = 82 |
| Flatulence | 2 (1.6) | 2 (2.4) |
| Foot fracture | 1 (0.8) | - |
| Forced expiratory volume decreased | 7 (5.6) | 6 (7.3) |
| Gamma-glutamyltransferase increased | 2 (1.6) | 2 (2.4) |
| Gastroenteritis viral | 2 (1.6) | 2 (2.4) |
| Gastrooesophageal reflux disease | 3 (2.4) | 1 (1.2) |
| Generalised oedema | - | 1 (1.2) |
| Genital pruritus female | 1 (0.8) | - |
| Genital rash | - | 1 (1.2) |
| Gingival pain | - | 1 (1.2) |
| Glossodynia | 2 (1.6) | - |
| Glucose tolerance impaired | - | 1 (1.2) |
| Glycosylated haemoglobin increased | 1 (0.8) | - |
| Gout | 1 (0.8) | - |
| Granulomatous liver disease | 1 (0.8) | - |
| Haematocrit decreased | 1 (0.8) | - |
| Haematuria | - | 2 (2.4) |
| Haemoglobin decreased | 1 (0.8) | - |
| Haemorrhage subcutaneous | - | 1 (1.2) |
| Haemorrhoids | - | 1 (1.2) |
| Head injury | 1 (0.8) | - |
| Hearing impaired | - | 1 (1.2) |
| Heart rate increased | 1 (0.8) | 1 (1.2) |
| Heart rate irregular | 1 (0.8) | - |
| Hepatic enzyme increased | 1 (0.8) | - |
| Herpes simplex | 2 (1.6) | 1 (1.2) |
| Humerus fracture | - | 1 (1.2) |
| Hyperglycaemia | 2 (1.6) | - |
| Hyperhidrosis | 5 (4.0) | 1 (1.2) |

## Common TEAEs Reported in Study 006 Patients – continued

| Table S16f | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| AEs preferred term | 75 mg TID N = 125 | 75 mg BID N = 82 |
| Hyperkalaemia | 1 (0.8) | - |
| Hypersensitivity | 1 (0.8) | - |
| Hypertension | 1 (0.8) | 1 (1.2) |
| Hypoaesthesia | 4 (3.2) | 1 (1.2) |
| Hypoglycaemia | 2 (1.6) | - |
| Hypoxia | 1 (0.8) | 2 (2.4) |
| Impetigo | - | 1 (1.2) |
| Incision site complication | 1 (0.8) | 2 (2.4) |
| Increased appetite | - | 1 (1.2) |
| Increased viscosity of bronchial secretion | 2 (1.6) | - |
| Influenza | 1 (0.8) | 1 (1.2) |
| Influenza like illness | 1 (0.8) | 1 (1.2) |
| Inguinal hernia | 1 (0.8) | - |
| Injection site cellulitis | - | 1 (1.2) |
| Injection site erythema | 1 (0.8) | - |
| Injection site pain | - | 1 (1.2) |
| Insomnia | 4 (3.2) | 2 (2.4) |
| Instillation site erythema | - | 1 (1.2) |
| Instillation site pain | 1 (0.8) | - |
| Intestinal obstruction | 1 (0.8) | - |
| Iron deficiency anaemia | - | 1 (1.2) |
| Joint effusion | 1 (0.8) | - |
| Joint sprain | 1 (0.8) | 2 (2.4) |
| Joint swelling | 2 (1.6) | 1 (1.2) |
| Lacrimation increased | - | 2 (2.4) |
| Laryngeal erythema | - | 1 (1.2) |
| Laryngeal pain | 1 (0.8) | - |
| Laryngitis | 3 (2.4) | 3 (3.7) |
| Lethargy | 1 (0.8) | - |
| Leukocytosis | 1 (0.8) | - |
| Ligament repair | 1 (0.8) | - |
| Limb discomfort | 1 (0.8) | - |
| Lip dry | 1 (0.8) | - |
| Lipase increased | - | 1 (1.2) |
| Liver function test abnormal | 2 (1.6) | - |

## Common TEAEs Reported in Study 006 Patients – continued

| Table S16g | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| AEs preferred term | 75 mg TID N = 125 | 75 mg BID N = 82 |
| Liver palpable subcostal | 1 (0.8) | - |
| Loss of consciousness | 1 (0.8) | - |
| Lower respiratory tract infection | - | 1 (1.2) |
| Lung consolidation | - | 1 (1.2) |
| Lung infection | 1 (0.8) | - |
| Lymphadenopathy | 2 (1.6) | 2 (2.4) |
| Malaise | 2 (1.6) | 3 (3.7) |
| Mental status changes | 1 (0.8) | - |
| Metrorrhagia | - | 1 (1.2) |
| Migraine | 1 (0.8) | - |
| Molluscum contagiosum | 1 (0.8) | - |
| Monocyte count increased | - | 1 (1.2) |
| Muscle spasms | 1 (0.8) | 2 (2.4) |
| Musculoskeletal chest pain | 6 (4.8) | - |
| Musculoskeletal pain | - | 2 (2.4) |
| Myalgia | 10 (8.0) | 5 (6.1) |
| Nasal mucosal disorder | 7 (5.6) | 6 (7.3) |
| Nasal oedema | 4 (3.2) | 7 (8.5) |
| Nasal polyps | 3 (2.4) | 1 (1.2) |
| Nasal turbinate abnormality | 1 (0.8) | - |
| Nasopharyngeal disorder | - | 2 (2.4) |
| Nasopharyngitis | 3 (3.7) | 6 (7.3) |
| Neck pain | 1 (0.8) | - |
| Nephrolithiasis | 1 (0.8) | - |
| Neutrophil count increased | - | 2 (2.4) |
| Night sweats | 2 (1.6) | 4 (4.9) |
| Ocular hyperaemia | 2 (1.6) | 1 (1.2) |
| Oedema peripheral | 2 (1.6) | 1 (1.2) |
| Oesophagitis | 1 (0.8) | - |
| Oral candidiasis | 4 (3.2) | 4 (4.9) |
| Oral mucosal exfoliation | 1 (0.8) | - |
| Osteoporosis | - | 1 (1.2) |
| Otitis media | - | 1 (1.2) |

**Common TEAEs Reported in Study 006 Patients – continued**

| **Table S16h** | **Number (%) of patients reporting AEs in study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg TID N = 125** | **75 mg BID N = 82** |
| Otoplasty | 1 (0.8) | - |
| Otosclerosis | 1 (0.8) | - |
| Ovarian cyst | 1 (0.8) | 1 (1.2) |
| Oxygen consumption increased | 2 (1.6) | - |
| Oxygen saturation decreased | 2 (1.6) | - |
| Pain | 6 (4.8) | 7 (8.5) |
| Pain in extremity | 6 (4.8) | 4 (4.9) |
| Pain in jaw | 1 (0.8) | - |
| Pallor | - | 1 (1.2) |
| Palpitations | - | 1 (1.2) |
| Paranasal sinus hypersecretion | 7 (5.6) | - |
| Pathogen resistance | - | 1 (1.2) |
| Periorbital oedema | 1 (0.8) | - |
| Pharyngeal erythema | 4 (3.2) | 2 (2.4) |
| Pharyngitis | 1 (0.8) | - |
| Phlebitis | 1 (0.8) | - |
| Pleurisy | - | 1 (1.2) |
| Pleuritic pain | - | 2 (2.4) |
| Pneumonia | - | 2 (2.4) |
| Poor venous access | - | 1 (1.2) |
| Portal hypertension | - | 1 (1.2) |
| Post procedural pain | 1 (0.8) | 2 (2.4) |
| Postnasal drip | 6 (4.8) | 6 (7.3) |
| Postoperative fever | - | 1 (1.2) |
| Prolonged expiration | - | 2 (2.4) |
| Protein total increased | - | 1 (1.2) |
| Pruritus | 4 (3.2) | 1 (1.2) |
| Pruritus generalised | 1 (0.8) | - |
| Pulmonary congestion | 2 (1.6) | - |
| Rales | 1 (0.8) | 4 (4.9) |

## Common TEAEs Reported in Study 006 Patients – continued

| Table S16i | Number (%) of patients reporting AEs in study 006 | |
|---|---|---|
| **AEs preferred term** | **75 mg TID N = 125** | **75 mg BID N = 82** |
| Rash | 7 (5.6) | 7 (8.5) |
| Rash erythematous | 1 (0.8) | - |
| Respiratory sighs | 1 (0.8) | - |
| Restlessness | - | 2 (2.4) |
| Rhinalgia | - | 1 (1.2) |
| Rhinitis | 6 (4.8) | 4 (4.9) |
| Rhinitis allergic | 3 (2.4) | - |
| Rhonchi | 6 (4.8) | 5 (6.1) |
| Rib fracture | 1 (0.8) | - |
| Shoulder pain | 2 (1.6) | 1 (1.2) |
| Sinusitis | 4 (3.2) | 1 (1.2) |
| Skin candida | - | 1 (1.2) |
| Skin discolouration | 1 (0.8) | - |
| Skin infection | 1 (0.8) | - |
| Skin laceration | 1 (0.8) | - |
| Skin lesion | 1 (0.8) | - |
| Sleep disorder | 1 (0.8) | 1 (1.2) |
| Sneezing | 4 (3.2) | 1 (1.2) |
| Soft tissue injury | 1 (0.8) | - |
| Sputum culture positive | 1 (0.8) | 1 (1.2) |
| Sputum decreased | 1 (0.8) | - |
| Sputum discoloured | 8 (6.4) | 1 (1.2) |
| Sputum retention | 1 (0.8) | - |
| Staphylococcal infection | 1 (0.8) | 1 (1.2) |
| Stenotrophomonas infection | 1 (0.8) | - |
| Stomach discomfort | 1 (0.8) | 2 (2.4) |
| Stomatitis | 3 (2.4) | - |
| Swelling face | 1 (0.8) | - |
| Swollen tongue | 1 (0.8) | - |
| Tachycardia | 1 (0.8) | 1 (1.2) |
| Tachypnoea | - | 1 (1.2) |

## Common TEAEs Reported in Study 006 Patients – continued

| **Table S16j** | **Number (%) of patients reporting AEs in study 006** | |
|---|---|---|
| **AEs preferred term** | **75 mg TID N = 125** | **75 mg BID N = 82** |
| Teratoma | 1 (0.8) | - |
| Testicular pain | 1 (0.8) | - |
| Thirst | 1 (0.8) | - |
| Throat irritation | 7 (5.6) | 2 (2.4) |
| Throat tightness | 1 (0.8) | - |
| Tinea pedis | 1 (0.8) | - |
| Tinnitus | 1 (0.8) | 2 (2.4) |
| Tongue disorder | 1 (0.8) | - |
| Tongue exfoliation | 1 (0.8) | 1 (1.2) |
| Tonsillar disorder | - | 1 (1.2) |
| Tooth extraction | 1 (0.8) | - |
| Toothache | 2 (1.6) | 2 (2.4) |
| Tremor | - | 1 (1.2) |
| Tympanic membrane disorder | 1 (0.8) | - |
| Tympanic membrane hyperaemia | 1 (0.8) | - |
| Ultrasound liver abnormal | - | 1 (1.2) |
| Umbilical hernia | - | 1 (1.2) |
| Upper respiratory tract infection | - | 2 (2.4) |
| Urinary incontinence | - | 1 (1.2) |
| Urticaria | - | 2 (2.4) |
| Vaginal discharge | 1 (0.8) | 1 (1.2) |
| Vaginal mycosis | 2 (1.6) | 2 (2.4) |
| Vertigo | 1 (0.8) | - |
| Vision blurred | 1 (0.8) | - |
| Vitamin A deficiency | 2 (1.6) | 1 (1.2) |
| Vitamin D deficiency | 1 (0.8) | 1 (1.2) |
| Vitamin E deficiency | 2 (1.6) | - |
| Weight gain poor | 2 (1.6) | - |
| White blood cell count increased | - | 2 (2.4) |

## TRAEs Reported in Study 006 Patients

| **Table S17b** | **Number (%) of patients reporting TRAEs in study 006** | |
|---|---|---|
| | **75 mg TID** | **75 mg BID** |
| **AEs preferred term** | **N = 125** | **N = 82** |
| Abdominal pain | - | 3 (3.7) |
| Acne | - | 1 (1.2) |
| Arthralgia | 3 (3.7) | 2 (2.4) |
| Asthenia | - | 2 (2.4) |
| Blood chloride decreased | - | 2 (2.4) |
| Chest pain | 1 (0.8) | - |
| Contusion | - | 1 (1.2) |
| Decreased appetite | 1 (0.8) | - |
| Dehydration | - | 1 (1.2) |
| Diarrhoea | - | 1 (1.2) |
| Dry mouth | 2 (1.6) | - |
| Dry throat | - | 1 (1.2) |
| Dysgeusia | 1 (0.8) | 1 (1.2) |
| Dyspepsia | - | 1 (1.2) |
| Dysphonia | 2 (1.6) | - |
| Ear congestion | 1 (0.8) | 2 (2.4) |
| Epistaxis | 1 (0.8) | - |
| Exercise tolerance decreased | 1 (0.8) | 1 (1.2) |
| Fatigue | 2 (1.6) | 2 (2.4) |
| Forced expiratory volume decreased | 1 (0.8) | 1 (1.2) |
| Gamma-glutamyltransferase increased | - | 1 (1.2) |
| Glossodynia | 1 (0.8) | - |
| Haemorrhage subcutaneous | - | 1 (1.2) |
| Headache | 4 (3.2) | 3 (3.7) |
| Increased appetite | - | 1 (1.2) |
| Insomnia | 1 (0.8) | - |
| Joint swelling | - | 1 (1.2) |
| Liver function test abnormal | 1 (0.8) | - |
| Musculoskeletal chest pain | 1 (0.8) | - |
| Musculoskeletal pain | - | 1 (1.2) |
| Myalgia | 1 (0.8) | - |
| Nasal congestion | 2 (1.6) | 2 (2.4) |

## TRAEs Reported in Study 006 Patients – Continued

| **Table S17c** | **Number (%) of patients reporting TRAEs in study 006** | |
|---|---|---|
| | **75 mg TID** | **75 mg BID** |
| **AEs preferred term** | **N = 125** | **N = 82** |
| Nasal mucosal disorder | - | 1 (1.2) |
| Nasal oedema | 1 (0.8) | - |
| Night sweats | - | 1 (1.2) |
| Non-cardiac chest pain | 2 (1.6) | 1 (1.2) |
| Oedema peripheral | - | 1 (1.2) |
| Oral candidiasis | - | 1 (1.2) |
| Oxygen consumption increased | 1 (0.8) | - |
| Pain | - | 1 (1.2) |
| Pain in extremity | - | 1 (1.2) |
| Palpitations | - | 1 (1.2) |
| Paranasal sinus hypersecretion | 1 (0.8) | - |
| Pharyngeal erythema | 2 (1.6) | - |
| Pharyngolaryngeal pain | 5 (4.0) | 5 (6.1) |
| Pleuritic pain | - | 1 (1.2) |
| Postnasal drip | 1 (0.8) | - |
| Pruritus | 1 (0.8) | - |
| Pulmonary function test decreased | 1 (0.8) | - |
| Pyrexia | 1 (0.8) | 1 (1.2) |
| Rash | 1 (0.8) | 1 (1.2) |
| Rhinorrhoea | 3 (2.4) | 2 (2.4) |
| Shoulder pain | 1 (0.8) | - |
| Sinus congestion | 2 (1.6) | - |
| Sinus headache | 1 (0.8) | - |
| Sneezing | 1 (0.8) | - |
| Stomach discomfort | - | 1 (1.2) |
| Stomatitis | 1 (0.8) | - |
| Swelling face | 1 (0.8) | - |
| Throat irritation | 2 (1.6) | 1 (1.2) |
| Throat tightness | 1 (0.8) | - |
| Tinnitus | 1 (0.8) | 2 (2.4) |
| Tongue exfoliation | 1 (0.8) | 1 (1.2) |
| Wheezing | 3 (2.4) | 2 (2.4) |

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/s/
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Menfo Imoisili
9/5/2008 03:03:05 PM
MEDICAL OFFICER

John Alexander
9/5/2008 03:10:55 PM
MEDICAL OFFICER

# Cross-Discipline Team Leader Review Memo

| | |
|---|---|
| **Date** | September 2, 2008 |
| **From** | John Alexander, MD, MPH |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA #** | NDA 50-814 |
| **Proprietary / Established (USAN) names** | Cayston® (Aztreonam for Inhalation Solution) |
| **Dosage forms / strength** | Powder for reconstitution (75 mg of aztreonam base), packaged with diluent (1 mL of Sodium Chloride 0.17% solution) |
| **Proposed Indication(s)** | 1. To improve respiratory symptoms and pulmonary function in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* |
| **Recommended:** | Approvable – Issue Complete Response Letter |

## 1. Introduction to Review

NDA 50-814 was submitted on November 16, 2007 for Cayston® (aztreonam for inhalation solution), a new (lysine) salt of aztreonam developed for treatment of patients with cystic fibrosis. The NDA was submitted by Gilead Sciences, Inc.

Aztreonam is a monobactam antibacterial (related to the beta-lactam antibiotics), approved for use in the US since 1986 as an intravenous antibacterial. Aztreonam is available as an arginine salt, marketed under the brand name Azactam®.

This memo will provide an overview of the NDA submission, but will address in more detail the clinical/statistical issues that are the main basis for the recommended action.

## 2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Azactam® (aztreonam for injection) has been in clinical use in the United States as an intravenous antibiotic since FDA approval in 1986. Azactam® is used for treatment of a variety of infections caused by Gram-negative bacteria, particularly *Pseudomonas aeruginosa*.

In March 2002, Corus Pharma, Inc. proposed development of an inhalation solution of aztreonam for treatment of cystic fibrosis patients, and received orphan drug designation. The sponsor submitted a pre-IND package in April 2002. Corus Pharma submitted the investigational new drug application (IND 64,402) for aztreonam for inhalation (AI) in April 2003. There were meetings and other interactions with the sponsor regarding the development program for AI. These interactions included several meetings to discuss the design of each of the phase 3 trials, the patient-reported outcome (PRO) tool used as primary endpoint in one study (study 007), and the endpoint of time to exacerbation of CF used as primary in the other (study 005). Gilead Sciences, Inc. acquired Corus Pharma in August 2006, completed the

phase 3 studies, and submitted the NDA. A letter documenting change of ownership for NDA 50-814 was submitted on August 9, 2007. Portions of the NDA for Cayston® (aztreonam for inhalation solution) were submitted under rolling review procedures. Nonclinical and quality portions of the NDA were submitted on July 14, 2006 and September 13, 2007. The remainder of the NDA was submitted on November 16, 2007, and included a request for priority review. However, the application was assigned a standard review in the filing letter dated January 10, 2008.

## 3. CMC/Microbiology/Device

The CMC review was conducted by Mark R. Seggel. A separate product quality microbiology review (PQMR) was conducted by Vinayak B. Pawar. The CMC reviewer considered the product ready for approval, though he noted that the product quality microbiology review was still pending at the time the CMC review was written. The PQMR was completed on August 27, 2008. The PQMR concluded that the NDA was approvable, pending resolution of questions related to sterility assurance for the drug product and diluent (see section 3.2).

### 3.1. General product quality considerations

The final drug product for Cayston® (aztreonam for inhalation solution) is supplied as a vial containing a sterile, lyophilized powder of 75 mg of aztreonam base with L-lysine in a 1:1.9 mole ratio. There are no other excipients. The diluent is 0.17% w/v sodium chloride solution, supplied in 1-mL ampules. When reconstituted, the aztreonam inhalation solution has an osmolality not exceeding 550 mOsm/kg and pH of 4.5-6.0. The drug product is supplied in a carton with a 28-day supply (84 vials) of lyophilized aztreonam and 88 ampules of diluent (four extra are provided in case of spillage).

The inhalation solution is delivered via a hand-held jet nebulizer manufactured by PARI Pharma. The jet nebulizer used in clinical trials and intended for use with the to-be-marketed formulation is based on PARI's e-flow nebulizer. The PARI e-flow has been cleared by CDRH as a general use nebulizer. Because of modifications to the product and labeling for the drug-specific nebulizer for use with Cayston®, PARI has submitted a supplemental 510 (k) for the Altair Nebulizer System. The Division has been working with CDRH and the Office of Combination Products to coordinate actions on both the NDA and the CDRH application for the device.

#### 3.1.1. Facilities review/inspection

The NDA application included (b) (4) as the manufacturing facility and Gilead Sciences as a testing facility. There is a separate facility for manufacturing the diluent, (b) (4) The sponsor added Gilead Sciences, Inc. in San Dimas, CA as a manufacturing facility, because of concerns about outstanding compliance issues with the (b) (4) facility early in the NDA review cycle. Gilead was added formally as a manufacturing facility in March 2008.

Ultimately, all facilities inspections for drug product manufacturing and testing sites were considered acceptable. Per the CMC review, the Office of Compliance gave an overall acceptable recommendation on July 2, 2008.

3.2. Other notable issues

The PQMR review provided a list of deficiencies that would need to be addressed for sterility assurance of the drug product and diluent. The information needed for support of drug product from Gilead Sciences, Inc. appears to be more extensive, likely related to the decision to add this facility during the NDA review. Though less information is needed to support product microbiology quality for drug product from the (b) (4) facility, there is still additional information needed for sterility assurance of the diluent from (b) (4)

***CDTL Comment**: The deficiencies cited in the PQMR review should be conveyed to the sponsor.*

## 4. Nonclinical Pharmacology/Toxicology

The pharmacology toxicology (P/T) review was conducted by Dr. Amy Ellis. The pharmacology reviewer had no objections to approval of the NDA. There are no outstanding P/T issues, aside from negotiation of product labeling.

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The active ingredient of this drug product (aztreonam) is a monobactam antibacterial. See the Clinical Microbiology section of this memo for further discussion of the pharmacological properties of the product. To support the development of Cayston® for use via inhalation, the sponsor conducted inhalational toxicology studies in rats and dogs. The sponsor also conducted a study in guinea pigs for pulmonary sensitization, tests in rabbits for dermal and eye irritation, and a carcinogenicity study in rats.

The inhalational studies showed that rats and dogs tolerated repeated doses of aerosolized aztreonam "without experiencing systemic toxicity or untoward effects on respiratory tissues".

4.2. Carcinogenicity

The sponsor conducted a 2-year carcinogenicity study of nebulized Cayston® in Sprague-Dawley rats. Drug or vehicle (30 mM NaCl in water) was delivered by nose-only inhalation. Estimated inhaled daily doses of aztreonam base were 0, 31, 56, and 120 mg/kg/day. The study was adequate and was considered negative for drug-related tumors.

4.3. Reproductive toxicology

The sponsor was not required to perform genotoxicity or reproductive toxicology studies of Cayston®. Instead, under a 505 (b)(2) NDA application, the sponsor relied on FDA's previous findings of safety and efficacy for Azactam® (aztreonam for injection) to support their product. As described in the labeling for Azactam®, genetic toxicology studies showed no evidence of mutagenic potential and reproductive toxicology studies performed using intravenous aztreonam showed no evidence of embryo/fetal toxicity, teratogenicity, or impaired fertility. Because studies with intravenous aztreonam provide systemic exposure to aztreonam that is far in excess of what would be achieved with delivery of Cayston® via inhalation, further genetic and reproduction toxicology studies with Cayston® were not considered necessary.

4.4. Other notable issues

None

## 5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Dr. Sarah Robertson. She concluded that the clinical pharmacology and biopharmaceutics information provided by the sponsor were acceptable, though the reviewer suggested that the 75 mg TID dose may not be the most efficacious. She recommended that "if the Sponsor is to complete an additional Phase 3 clinical trial in CF patients, two dosing regimens of AI should be evaluated – 75 mg TID and 150 mg BID".

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

In adult CF patients given aztreonam via inhalation, the mean plasma $C_{max}$ was 419 ng/mL, low compared to the $C_{max}$ of 90 µg/mL following 1 g of intravenous aztreonam. Plasma $T_{max}$ was seen <1 hour after start of inhalation. The terminal elimination half-life from plasma of 2.1 hours was similar for inhalational and intravenous delivery. Only 10% of the inhalational dose was recovered unchanged in urine over 24 hours, compared to 60-65% for an IV dose. This suggests that absorption from the lung is low.

Sputum concentrations of aztreonam following inhalation are highly variable, likely related to the pathophysiology of CF and to the use of thick, expectorated sputum as the test sample. The median sputum concentration of aztreonam was 383 µg per gram of sputum (range 86-2170) in adult CF patients 10 minutes after a single 75 mg dose of Cayston®. Sputum concentrations increased approximately proportional to dose for a 150 mg dose, but further increases were minimal for a 225 mg dose. Sputum concentrations appeared to be consistently lower for adolescent CF patients compared to adults at all dose groups. For adolescents, the increasing doses of Cayston® (75,

150, 225 mg) did not appear to increase sputum concentrations, though variability was great. No accumulation of aztreonam was noted in plasma or sputum of CF patients with multiple doses up to 225 mg BID.

Beta-lactam antibiotics, including aztreonam, are considered to display time-dependent actions with systemic treatment of infections. Time above the minimum inhibitory concentration (T>MIC) is typically used as a pharmacodynamic measure for beta-lactams; higher T>MIC in the serum is associated with greater treatment effect for systemic antibiotics. It is unclear how this information would apply to inhaled aztreonam, acting locally against *Pseudomonas aeruginosa* in the lungs of CF patients. The clinical pharmacology review provides a discussion of the low T>MIC seen for Cayston® in the lung, based on repeated samples of expectorated sputum. The observed T>MIC for 75 mg of aztreonam given TID was only 12%. However, the significant variability of aztreonam concentrations in sputum makes it difficult to draw conclusions about this PK/PD parameter.

5.2. Drug-drug interactions

Because there appears to be limited absorption from the lung, and there are no clinically significant drug interactions reported in labeling for Azactam®, significant drug-drug interactions with other systemic medications are not expected for Cayston®.

The clinical pharmacology review included discussion of Cayston® given with or without prior bronchodilator treatment. There was no apparent effect of the addition of the bronchodilator on sputum or serum concentrations of aztreonam.

5.3. Pathway of Elimination

For intravenous aztreonam, 60-65% is excreted unchanged in urine and approximately 7% is hydrolyzed to a metabolite with an open beta-lactam ring. For Cayston®, 10% of the administered dose is excreted unchanged in urine over 24 hours.

5.4. Demographic interactions/special populations

The differences in sputum pharmacokinetics for adolescent and adult CF patients were discussed in section 5.1 above. There were no apparent adverse effects of lower sputum concentrations, since it appeared that adolescents had better responses to treatment in phase 3 trials. Elderly patients were not studied with Cayston® since the drug is intended for CF patients, a condition resulting in early mortality. Mean age at death is under 40 years for CF patients in the US.

Because of limited systemic absorption, no dosage adjustment is considered necessary for patients with renal impairment. The clinical pharmacology review discusses in detail how expected serum concentrations of aztreonam in patients with severe renal impairment who receive Cayston® are unlikely to approach normal therapeutic concentrations for IV aztreonam.

For patients with hepatic impairment, limited hepatic metabolism as well as limited systemic absorption make need for dosage adjustment unlikely.

Roughly equal numbers of males and female CF patients were included in the PK studies. No gender effects were noted in the clinical pharmacology review. Since CF occurs mainly in Caucasians, the number of African American or Hispanic patients in PK studies was limited.

5.5. Thorough QT study or other QT assessment

Intravenous aztreonam has not been associated with QT prolongation, and the systemic aztreonam exposure from inhalation of Cayston® is much lower by comparison. Therefore, this product is not expected to have any significant effects on the QT interval of treated patients.

5.6. Other notable issues

The clinical pharmacology review notes the results of a phase 3 study (005), suggesting a regimen effect favoring BID treatment. (The study is discussed in section 7 of this memo.) She recommends exploration of 150 mg BID as an alternative dose that might demonstrate greater effect with better tolerability than the 75 mg TID dose.

## 6. Clinical Microbiology

6.1. General considerations

The clinical microbiology review was conducted by Dr. Peter Coderre. Aztreonam is a monobactam antibacterial, related to the larger class of beta-lactam antibiotics. Aztreonam inhibits bacterial cell wall synthesis through actions on specific "penicillin-binding proteins" responsible for elongation and cross-linking of peptidoglycan chains.

Aztreonam is active mainly against Gram-negative bacteria, including *Pseudomonas aeruginosa* (PA), the major pathogen in the lung of CF patients. Strains of PA have become increasingly resistant to antibiotics in both CF and non-CF populations. The clinical microbiology review notes that the percent of PA isolates considered susceptible to aztreonam (MIC <8 μg/mL) decreased from 80% in 1995 to 68.6% in 2006. However, this susceptibility criterion is based on serum concentrations achieved with intravenous treatment.

The clinical microbiology review describes in detail the mechanism of action, spectrum of activity, and mechanisms of resistance for aztreonam. The review also discusses the clinical microbiology results for the studies of Cayston® in CF patients. Microbiological outcomes include the changes in colony forming units (CFU) of *Pseudomonas aeruginosa* per gram of sputum measured on a $\log_{10}$ scale; appearance of

other pathogens on sputum culture (*S. aureus*, *B. cepacia*, *S. maltophilia*, or *A. xylosoxidans*); and changes in aztreonam $MIC_{50}$ and $MIC_{90}$ for PA isolates. The clinical microbiology reviewer states that patients in the treatment arm "had lower or comparable PA loads in sputum, showed no increases in other pathogens associated with CF and had pathogens with similar $MIC_{90}$s at baseline and end of treatment, that is there were no changes in susceptibility to aztreonam in *P. aeruginosa* isolates". However, these microbiological outcomes did not show any correlation with clinical outcomes. This lack of correlation was also reported for TOBI, the approved inhalational aminoglycoside used in CF patients.

6.2. Discussion of primary and secondary reviewers' comments and conclusions

The clinical microbiology reviewer made no recommendation on approvability of the NDA application. Instead, he deferred to the clinical and statistical reviewers. The reviewer did so because of the lack of correlation of microbiological outcomes with clinical responses. The microbiology review states "As none of the examined microbiology endpoints correlate with clinical outcomes, this Reviewer believes the clinical endpoints should be the deciding factors in the determination of clinical efficacy of AI."

6.3. Notable issues

The clinical microbiology review does not include recommendations for product labeling, based on the expectation that another study will be needed. If another trial is conducted, then the microbiology information may require changes.

## 7. Clinical/Statistical

The clinical program for aztreonam for inhalation (AI) solution was developed in consultation with the Division of Anti-Infective and Ophthalmology Products (DAIOP). The clinical program included 2 phase 1 studies of ascending doses in healthy volunteers or CF patients. Based on phase 1 results, the sponsor conducted a phase 2 exploratory study of 75 mg or 225 mg of aztreonam for 14 days compared to placebo. This phase 2 study used change in forced expiratory volume in one second ($FEV_1$) as the primary endpoint, but was not able to show statistically significant differences for aztreonam versus placebo. Further, there appeared to be a trend toward increase in drug-related cough with the higher dose of aztreonam, though this was based on small numbers. Therefore, the sponsor elected to move forward with studies of the 75 mg dose, and the Division concurred.

The clinical program included two placebo-controlled phase 3 studies intended to provide evidence of efficacy (studies 005 and 007), and a follow-on study (006) intended mainly to provide additional safety information on the use of multiple treatment courses of inhaled aztreonam. The following table provides a brief description of the phase 3 studies, specifically highlighting the differences in primary endpoint, and treatment regimen.

During the clinical development program, there was a special protocol assessment performed for study 005. The FDA letter included a recommendation that randomization of patients be done at visit 3, just prior to beginning study drug treatment, rather than at visit 2. The significance of this recommendation will be discussed with the efficacy results for this study.

| **Study Identifier** | **Objective(s)** | **Study Design and Type of Control** | **Test Product; Dose Regimen** | **Number of Subjects in Safety Population** | **Duration of Treatment** |
|---|---|---|---|---|---|
| CP-AI-005 | Assess safety and efficacy of AI; primary endpoint – time to need for inhaled or IV antibiotics | Double-blind, placebo-controlled; 28 days TSI (open label) followed by AI or placebo | AI; 75 mg BID or TID; inhalation | 211 (69 BID AI, 66 TID AI, 38 BID placebo, 38 TID placebo) | 28-day run-in of TSI, 28 days of AI, 56 days of follow-up |
| CP-AI-007 | Assess safety and efficacy of AI; primary endpoint – change in CFQ-R respiratory symptoms domain (Day 0 to Day 28). | Double-blind, Placebo-controlled | AI; 75 mg TID; inhalation | 164 (80 AI, 84 placebo) | 28 days of AI, 14 days of follow-up |
| CP-AI-006 | Assess long term safety of AI; primary endpoint – AEs, airway reactivity, vital signs, labs. Secondary disease-related endpoints include FEV1 and CFQ-R. | Open-label follow-on study (patients from CP-AI-005 and -007). Patients receive AI according to the same regimen (BID or TID) previously assigned | AI: 75mg BID or TID; inhalation | 207 at the 01 March 2007 cutoff (82 BID, 125 TID) | Up to nine 28-day courses of AI, each course followed by 28 days off treatment |

The clinical review was conducted by Dr. Menfo A. Imoisili. The statistical review was conducted by Dr. Christopher Kadoorie. The reader is referred to those documents for detailed analyses of the phase 3 studies. This memo will briefly summarize findings from studies 005 and 007.

## 7.1. Efficacy

### 7.1.1. Dose identification/selection and limitations

The sponsor's proposed dose is 75 mg (aztreonam base) via inhalation given TID. The dose was chosen based on findings from a phase 2 study as discussed in section 7 above. The 75 mg TID dose was studied in both phase 3 clinical studies.

7.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The two main studies supporting efficacy of AI are studies 005 and 007.

**Study 005**

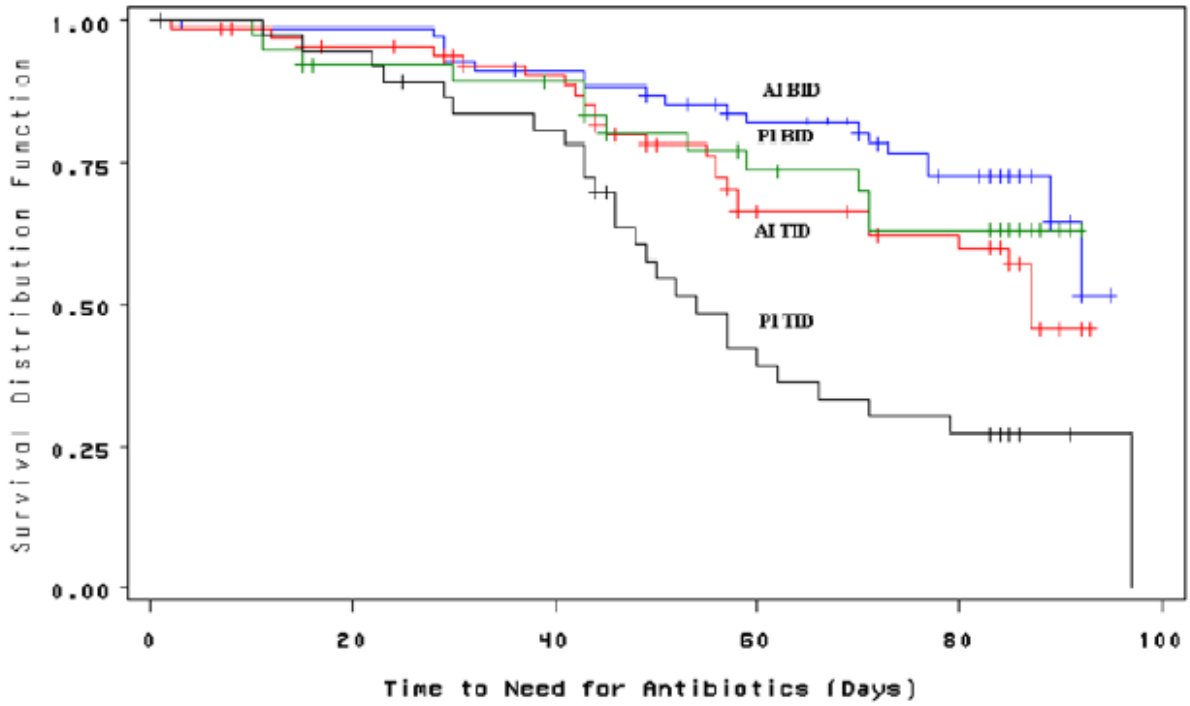
Study 005 enrolled CF patients ≥6 years of age with $FEV_1$ between 25% and 75% predicted and *Pseudomonas aeruginosa* in sputum. The study evaluated time to exacerbation of CF after patients received a 28 day course of TOBI (started at study visit 2), followed by a 28 day course of AI or placebo (started at study visit 3). The occurrence of an exacerbation was to be based on patients reporting at least one of four symptoms: increased cough, increased sputum/chest congestion, decreased exercise tolerance or decreased appetite. Study 005 included both an AI 75 mg BID and 75 mg TID dose group. Placebo patients received aerosol placebo BID or TID. Patients were randomized in a 2:2:1:1 ratio to these groups respectively. Fewer patients were randomized to the placebo groups based on recognition that CF is a rare condition, and the expectation that the placebo groups' results could be pooled. Patients were randomized at study visit 2, just prior to TOBI treatment, and 28 days prior to receiving AI or placebo. Patients were evaluated for symptoms of exacerbation at follow up visits every 2 weeks through 84 days from the start of AI or placebo. Secondary endpoints included change in CFQ-R, as described for study 007 below, and change in $FEV_1$ and other lung function parameters, measured by spirometry. Sputum cultures were also obtained for quantitation of *Pseudomonas aeruginosa* and identifications of other potential pathogens.

As detailed in the clinical and statistical reviews, the sponsor was able to demonstrate a significant difference in their primary endpoint comparing pooled AI treatment (BID or TID) to pooled placebo. However, this comparison involved pooling of the two AI treatment groups and the two placebo groups, which can be problematic if there are significant differences in the pooled treatment arms. There did appear to be significant differences by treatment group for the placebo, as can be seen in the figure on the following page. The figure shows the survival distribution function for time to need for antibiotics for the four separate treatment groups: AI BID, AI TID, Placebo BID, and Placebo TID. It is apparent from the figure that time to need for antibiotics differed in the placebo TID group from the other three groups. Significant differences between the pooled AI and pooled placebo were driven mainly by the results for the placebo TID group. From the figure, it appears that the placebo BID group performed slightly better than the AI TID group in this primary endpoint measurement. The results appear to show a regimen effect, with the placebo BID group performing significantly better than the placebo TID group.

Further investigations suggest two possibilities. First, there is the possibility of a regimen effect with BID placebo showing significantly better outcomes than the

TID placebo, and AI BID treatment showing a trend toward better outcome than the AI TID group. However, there is no clear mechanism for the significant differences in the placebo BID and TID groups. While poorer tolerance of a TID regimen might result in worse pulmonary function or increased symptoms during treatment, it is not clear how this would result in a difference between groups in occurrence of exacerbation symptoms starting around 2 weeks after study drug treatment was stopped.

The second possible explanation relates to the long period of time (28 days) between randomization (visit 2) and start of study drug treatment (visit 3). Although all patients received a course of TOBI between visits 2 and 3, it appears that there were differences in response, so that the treatment groups were no longer similar at the time of study drug treatment.




Regardless of the explanation for the differences in placebo groups, the results make it clear that pooling the two placebo groups is inappropriate. It is unknown whether the true placebo response in this study would be more like the TID placebo or the BID placebo. Given these findings, there are significant concerns about the ability to interpret the results of this trial. The study did not provide substantial evidence of the efficacy of aztreonam for inhalation.

**Study 007**

Study 007 also enrolled CF patients ≥6 years of age with $FEV_1$ between 25% and 75% predicted and *Pseudomonas aeruginosa* in sputum, but involved a different

study design from study 005. The primary objective of the study was to demonstrate a difference in CF symptoms with treatment, using the respiratory domain of the cystic fibrosis questionnaire-revised (CFQ-R) as a patient-reported outcome (PRO) tool. Patients were randomized in a 1:1 ratio to receive AI 75 mg TID or placebo. The study involved 5 visits: a screening visit (V1) up to 14 days before drug treatment; a baseline visit (V2) where patients began AI/placebo treatment; mid-treatment (V3) and end-of treatment (V4) visits at 14 and 28 days after start of treatment; and a follow-up visit (V5) at day 42. There was no TOBI pretreatment in this study. Along with evaluation of the change in CFQ-R, the study evaluated pulmonary function and microbiological changes in sputum as secondary endpoints.

The primary analysis for this trial compared change in scores for the respiratory domain of the CFQ-R for patients receiving AI 75 mg TID or placebo TID. The change in the CFQ-R respiratory domain in AI TID patients (n=84) was 7.8 versus -1.9 for placebo patients (n=80). This difference was statistically significant with a p-value of 0.0005. The treatment difference is larger than the minimal clinically important difference (MCID) of 5 established for this score in the validation of the PRO. As a separate responder analysis the sponsor used this MCID to categorize individual patients as improved (change in CFQ-R >5), unchanged (change between -5 and 5) or worsened (change <-5). Using these criteria, 56% of patients in the AI group improved versus 37% of placebo patients. Worsening was reported for 25% of AI patients versus 45% in the placebo group. These differences in categorical response were statistically significant. Though less than the change at day 28, there did appear to be some sustained effect on symptoms at day 42, as measured by CFQ-R.

Consistent with these findings, there was also a statistically significant difference in $FEV_1$ at day 28. The mean adjusted change in $FEV_1$ % predicted for the AI group was 7.9% and for placebo was -2.4%. The difference of 10.3% was statistically significant with a p-value <0.0001. At day 42, the difference between treatment groups in $FEV_1$ was smaller (5.7%), but still statistically significant (p=0.0024). There was also a significant difference between treatment groups in the number of colony forming units of *Pseudomonas aeruginosa* from baseline to day 28. Despite concerns related to the use of the CFQ-R as a PRO tool (specifically, the potential for recall bias from the 2-week recall period), the findings from this trial provide evidence for the efficacy of 75 mg of AI given TID for 28 days.

7.1.3. Other efficacy studies

A small phase 2 study was conducted (study 003) evaluated change in $FEV_1$ as a primary endpoint, but was unable to demonstrate a statistically significant treatment difference between the AI groups (75 mg or 225 mg) and placebo. While the follow-on study (006) did include measurements of change in CFQ-R, pulmonary function, and sputum microbiology, the study can not be used as

supportive evidence of efficacy. Any efficacy conclusions are limited by the open-label design and the comparison of non-randomized groups continuing to receive treatment after studies 005 or 007.

### 7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

The clinical and statistical reviewers are in agreement on the main results for the two trials. For study 005, the study failed to provide substantial evidence of efficacy for AI. The primary outcome was time to need for antibiotics based on the presence of pre-defined symptoms of a CF exacerbation. The results showed a large regimen effect (BID > TID) such that the results for placebo BID regimen appeared slightly better than the AI TID regimen. The study results were considered not interpretable because of concerns that the time between randomization and study drug treatment caused imbalances, or that there was a true regimen effect causing better outcomes for patients treated BID.

Study 007 was successful in demonstrating a treatment effect of the AI 75 mg TID regimen on improving respiratory symptoms as measured by the respiratory domain of the CFQ-R. Significant improvements in pulmonary function test were also seen for patients in the study. The study was not able to demonstrate significant differences in time to need for antibiotics, though the short follow-up made it unlikely that differences would be seen. Some limitations of this study were noted, including questions about recall bias related to the two-week recall period used in the questionnaire and differences in questionnaires for young children (<14 years). Stronger responses were also seen for adolescents than for adults, and for patients with higher baseline $FEV_1$ (>50%).

All the clinical and statistical reviewers agree that an additional trial is needed to support the effectiveness of AI for treatment of CF patients. What remains unresolved is whether the study needs to address the questions about a BID regimen effect, should provide evidence on time to need for exacerbations, or could be based solely on symptoms of CF and pulmonary function testing. As CDTL, I recommend that the sponsor be asked to perform an additional study to support the efficacy of the product. Recognizing that cystic fibrosis is a rare condition, I believe it is reasonable to evaluate whether an ongoing trial for the European Union could provide additional evidence of efficacy. It is my opinion that the regimen effect seen in study 005 is a spurious finding, likely related to imbalances between groups after randomization. Therefore, I would not insist on additional studies of the BID regimen. I would prefer to see evidence that product treatment led to delay in time to need for additional antibiotics, rather than relying solely on change in CFQ-R and pulmonary function testing. However, both of these outcomes can still be measured in a trial whose primary endpoint is time to need for antibiotics.

7.1.5. Pediatric use/PREA waivers/deferrals

Because of orphan drug designation for this product, this product is exempted from any pediatric requirements. The sponsor's studies included some pediatric patients with cystic fibrosis. In the phase 3 trials (005 and 007), there were 25 patients in the 6-12 year age group and 58 patients in the 13-17 year age group. There were 55 pediatric patients who received aztreonam treatment (BID or TID) in these trials. Pediatric patients were approximately 22% of the study population.

7.1.6. Discussion of notable efficacy issues

An additional study is needed to support efficacy of AI for treatment of cystic fibrosis patients. As discussed in section 7.1.4 above, only one study (007) provided support for efficacy of AI. As noted by the sponsor during meetings in July and August of 2008, there was some discussion during the clinical development program about use of "one study" as a pivotal trial with support from the results of another trial. Early in the development program the sponsor had expected that study 005would be the pivotal trial with confirmatory evidence from the phase 2 trial (study 003). Because study 003 was unsuccessful in demonstrating differences in $FEV_1$ between the two doses studied and placebo, the sponsor went on to develop another trial of placebo controlled trial of TID treatment (study 007). The sponsor expressed concern about the study design for 007 (then referred to as study 004), because of uncertainty about success with the CFQ-R endpoint. At the time of the end-of-phase 2 study on November 23, 2004, the sponsor asked about failure of study 007 and reliance on study 005 alone (not reliance on study 007). The question and response was as follows:

> "If the pivotal Phase 3 study (CP-AI-004) fails, could the supportive study (CP-AI-005) be considered an alternate pivotal study?"
>
> "Given the Sponsor's current plans for one pivotal study and one supportive study, the Division suggested that it would depend on the "robustness" of the 005 results. If the robustness of the study was appropriate, then the indication would be limited to the design/endpoints of this study. The Phase 2 data were supposed to provide the supportive study results for the pivotal phase 3 study of 225 mg of AI, but did not achieve this objective. At issue is the ability of the Phase 3 studies to support one another in the event that the 005 study "hits" its primary endpoint and the 004 study "misses" its primary endpoint. The Division would prefer to see that both studies provide consistent results of the effectiveness of the proposed dose regimens of AI (75 mg BID or TID for 28 days)."

The points that I want to make about this response are:

- The discussion of reliance on a single pivotal trial was based on reliance on "robust" results on the study evaluating time to CF exacerbation. These CF

exacerbations include patients who are hospitalized or otherwise require intravenous treatment for their symptoms. This is not the same as reliance on a single study based on change in CF symptoms.

- The response pointed out that the sponsor's previous plan had involved a single pivotal trial of a 225 mg dose, with additional support from the phase 2 study (003). However, the phase 2 study did not achieve its objective. It should be clear from this discussion, that the lack of confirmatory evidence from the phase 2 trial was the basis for need for additional trials.
- The response is also clear about the preference that both studies provide consistent results of the effectiveness of the proposed AI regimens (at that time both the BID and TID regimens were being contemplated). The response notes that the issue is related to the ability of the trials to support the results of the other.

It should be clear based on this interaction that the Division was expecting both phase 3 trials to provide evidence of effectiveness although the interaction did leave open the potential for robust results from study 005, with some support from the other trial if the CFQ-R endpoint failed.

## 7.2. Safety

### 7.2.1. General safety considerations

The clinical review by Dr. Menfo A. Imoisili includes a detailed discussion of the safety findings for inhaled aztreonam.

As noted previously, this product is a new formulation of an existing systemic antibiotic, Azactam® (aztreonam for injection). FDA's prior findings of safety for intravenous aztreonam support the conclusion that minimal systemic adverse effects are expected for Cayston® (aztreonam for inhalation solution). However, there is a risk of hypersensitivity reactions, as described in the Warnings for Azactam (see section 7.2.4 on immunogenicity below.) The studies of Cayston® were still expected to include monitoring for systemic adverse events (AE) as well as local AE of the lung.

The studies included 537 individuals who received AI in single or multiple doses, and 519 were cystic fibrosis patients. There were 215 CF patients treated with AI (BID or TID for 28 days) in the two phase 3 efficacy trials. There were 207 CF patients treated with multiple 28 day courses of AI in the follow-on study (006). While this database is relatively small for most NDA applications, I consider it reasonable in size for this application. There is supportive evidence from the known safety profile for intravenous aztreonam, and the adverse reactions seen in the submitted trials did not raise significant drug-related safety concerns.

7.2.2. Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

In general, there were very few adverse reactions attributable to AI or more frequent than placebo in the controlled trials.

Deaths – There was one death in the course of the follow-on trial (006) in a patient who received eight 28-day treatment courses of AI 75 mg BID (the first as part of study 005). The patient had four hospitalizations for hemoptysis over the 17 months of her participation in the follow-on study. Two embolization procedures were performed at her first hospitalization. She died approximately one month after the last course of AI treatment with massive hemoptysis and cardiac arrest.

Unfortunately, hemoptysis is not a rare occurrence in patients with CF. This represents a complicated case with little suggestion of association of hemoptysis with AI treatment. The investigator did not consider the episodes of hemoptysis to be drug related, and the medical officer concluded that "the death did not appear to be causally related to the receipt of AI". Hemoptysis was reported as an SAE in one AI TID patient and one placebo patient in the controlled phase 3 studies.

Serious Adverse Events – Cough and productive cough were the most common SAE. The rates of these SAE were comparable across treatment arms. Other SAE were reported at such low frequencies that comparisons of SAE rates were not meaningful. The only SAE considered by investigators to be treatment related occurred in a placebo patient.

Discontinuations – Drug-related or study procedure-related AE leading to study discontinuation were more frequent in placebo patients.

General AE – Cough was the most frequent treatment-related AE, and was reported more frequently in patients who received AI TID than placebo (17% vs. 8%). Fever as an AE was also reported more frequently for AI TID than placebo patients (13% vs. 10%).

Laboratory Testing – Hematological abnormalities were reported at similar rates for AI and placebo patients. None were considered related to treatment. Hyperglycemia was also noted at similar frequencies in AI and placebo patients. There were two patients with hypoglycemia (glucose <40 mg/dL); one patient received AI TID and the other received placebo BID. Elevations in ALT or AST were generally less than 3 times the upper limit of normal (ULN). Elevations >3x ULN typically occurred in patients with abnormal baseline values. There were no cases that met Hy's law.

7.2.3. Safety update

Non-contributory

7.2.4. Immunogenicity, where pertinent

Similar to other beta-lactam antibiotics, hypersensitivity reactions have been reported with use of systemic aztreonam. As described in the product label for Azactam®, the risk of cross-reactivity with other beta-lactams appears to be less for aztreonam. Hypersensitivity reactions to aztreonam have been reported in cystic fibrosis patients, though they appear to occur at lower rates than hypersensitivity to other beta-lactams. There were no reports of serious hypersensitivity reactions in the studies conducted with AI, but patients with histories of hypersensitivity to aztreonam were excluded. Cayston® should be contraindicated in any patients with a history of hypersensitivity to aztreonam.

7.2.5. Special safety concerns

No special safety concerns were identified.

7.2.6. Discussion of primary reviewer's comments and conclusions

The primary reviewer's conclusions on safety were the basis for the safety findings discussed in section 7.2.2 of this memo. No significant safety concerns in relation to any of these findings were raised by the clinical reviewer. Since additional information is needed to support the effectiveness of AI in CF patients, no conclusions regarding the overall risk/benefit could be drawn.

The CDTL considers the adverse events that seemed related to treatment to be relatively minor. Adverse events related to local pulmonary effects (cough and chest discomfort) were more frequent in AI patients than placebo. The most serious AE expected for aztreonam would be related to hypersensitivity reactions, though such events have not yet been reported with Cayston® treatment. Serious hypersensitivity has been reported with intravenous aztreonam treatment.

7.2.7. Pre-Approval Safety Conference

A pre-approval safety conference was not held. An additional study to support effectiveness is considered necessary before the product can be approved.

7.2.8. Discussion of notable safety issues

Additional safety information will be provided from the additional phase 3 trial requested of the sponsor. This will need to be evaluated for consistency with AE results for the studies in this NDA submission.

## *8.* Advisory Committee Meeting

There was no advisory committee meeting held for this product.

## 9. Other Relevant Regulatory Issues

This NDA was submitted as a 505 (b)(2) application for Cayston (aztreonam for inhalation). The sponsor for this application is relying in part on FDA's previous findings of safety and efficacy for Azactam® (aztreonam for injection). Specifically, the sponsor is relying on information about the genetic toxicology, reproductive toxicology, and clinical safety of aztreonam (as described in the Azactam® label) for approval of the proposed product. Although Cayston is a lysine salt and Azactam® is an arginine salt, this information about Azactam is relevant to Cayston, because they both have the same active ingredient. The clinical safety information for Azactam is relevant to Cayston, since the systemic exposure to aztreonam from the inhaled product is lower than that seen with use of the intravenous product.

The sponsor for Cayston (aztreonam for inhalation) was required to conduct additional studies (as described in the various NDA reviews) to support the NDA application for the product in its intended use. Patent certifications for aztreonam were submitted in the NDA. The product was cleared for action by OND staff as a 505 (b)(2) NDA.

## 10. Financial Disclosure

There were no financial disclosure issues identified in this application. The sponsor completed FDA form 3454 indicating no financial arrangements, or other significant payments with investigators (in studies 003, 005, 007, and 006), and investigators reported no proprietary interest or significant equity in the sponsor.

## 11. Labeling

### 11.1. Proprietary name

DMETS had raised originally raised objections to the proposed proprietary name of Cayston in a review during the IND phase. The objection was based on orthographic similarity to Capoten. With the NDA, the sponsor asked for re-consideration of Cayston, based on the differences in indication, formulation, strength, route of administration, and packaging. They also noted little use by pharmacists of Capoten; instead the generic name captopril is typically used. Also, Cayston is typically expected to be prescribed through specialty pharmacies to CF patients, and have few prescriptions given its orphan drug designation.

In the review dated May 12, 2008, DMETS reversed their previous recommendation and stated they do not object to the name Cayston. Re-evaluation of the trade name within 90 days prior to the approval will be needed if the sponsor responds to the complete response letter.

11.2. Physician labeling

The regulatory project manager conducted a labeling review for consistency with the physician's labeling rule format. Physician labeling was not discussed for this application since the clinical and statistical reviewers recommended that an additional study to support the effectiveness of the product is needed. Significant changes in proposed labeling are expected with resubmission, in order to incorporate the results of the additional studies.

11.3 Carton and immediate container labels

Cayston (aztreonam for inhalation) is provided as a lyophilized powder in single use glass vials with a rubber stopper. The single use vials of powder are packaged together with low density polyethylene (LDPE) ampules containing 1 mL of 0.17% sodium chloride solution. Vials and LDPE ampules are packaged in 2 week and 28 day kits.

A labeling review (dated May 29, 2008) for the carton and container packaging was completed by DMETS. Recommendations were conveyed to the sponsor modifications to carton and immediate container labels. These included modifications for readability of the diluent ampules that are packaged with the vials of aztreonam. The sponsor has made revisions based on these recommendations, but requested other changes. Final agreement on the carton/container labeling was still pending at the time this memo was written.

11.4 Patient labeling/Medication guide

A medication guide is not considered necessary for this product. Patient labeling should be addressed together with the physician labeling.

## 12. DSI Audits

Clinical inspections were requested for four US sites, two each for the two pivotal studies (005 and 007). These were routine inspections of large sites in the two trials. (It should be noted that the sites enrolled only 9-12 subjects each, because CF is a rare disease and the studies involved multiple investigators enrolling very few patients.)

The clinical inspection summary (CIS), dated June 19, 2008, concluded that the studies appeared to have been conducted adequately and the data in support of the NDA appear reliable. The CIS stated that final classifications were "no action indicated" (NAI) for three of the four sites, and that the interim classification was NAI for the fourth. Final classification was pending for the 4$^{th}$ site, awaiting the final Establishment Inspection Report. NAI letters were issued in July for all four of the clinical inspection sites.

## 13. Conclusions and Recommendations

13.1. Recommended regulatory action

There is insufficient evidence of effectiveness for Cayston (aztreonam for inhalation solution) to recommend approval at this time. I concur with the recommendations of the review team to request an additional trial demonstrating the effectiveness of the product for treatment of cystic fibrosis patients. I would recommend that the primary endpoint of the trial demonstrate effectiveness of the 75 mg AI TID dose in delaying the time to need for antibiotics due to pre-defined symptoms. The study should also include changes in $FEV_1$ and the respiratory domain of the CFQ-R from baseline to end of study drug treatment as secondary endpoints.

My recommendation is to include proposals for studying the 150 mg BID regimen only as an option. It is my opinion that the data from the phase 2 study (CP-AI-003) did not demonstrate added benefit of 225 mg of AI given BID over 75 mg of AI given BID. Further, support for a 150 mg AI BID regimen would require two efficacy studies, with sufficient safety data to support the higher dose.

In addition, the deficiencies noted in the product quality microbiology review should be addressed by the sponsor to provide sterility assurance for the drug product and diluent.

13.2. Safety concerns to be followed postmarketing

Not Applicable – I do not recommend approval of Cayston® at this point.

13.3. Risk Minimization Action Plan, if any

13.3.1. General considerations on the need for, and goals of, any RiskMAP beyond standard labeling and pharmacovigilance. If a RiskMAP has been instituted, then details of the RiskMAP objectives and procedures should be described here.

The safety review did not identify adverse reaction that would require anything beyond standard labeling and pharmacovigilance.

13.3.2. Important issues related to the RiskMAP

Not Applicable

13.4. Postmarketing studies, voluntary or required (e.g., under PREA, Subpart H)

Not Applicable

13.5. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)

The clinical evidence provided by one of the two pivotal studies (study 007) was adequate to establish the efficacy of AI for use in the treatment and improvement of respiratory signs and symptoms and lung functions in CF patients with chronic Pseudomonas aeruginosa infection. However, we do not accept the results of study 005 as adequate evidence to support study 007 data. Therefore, another study is recommended to provide adequate evidence to support study 007 data for possible approval of AI.

Before the application may be approved, it will be necessary for you to perform adequate and well controlled Phase 3 study to demonstrate:

- A delay in the Time to Need for IV or Inhaled Antibiotics due to Pre-defined Symptoms
- Changes in CFQ-R Respiratory Domain Scores and changes in FEV1 at Day 28 should also be measured as secondary endpoints.
- A sequential testing procedure or other methodologies may be considered to control for the overall type-I error rate due to multiple testing.

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/s/
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John Alexander
9/15/2008 06:34:10 PM
MEDICAL OFFICER