

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
050814Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Memorandum to File
NDA 50-814 Cayston[®] (aztreonam for inhalation solution)

Date: February 12, 2010

From: John Alexander, MD, MPH
Cross-Discipline Team Leader (CDTL) for NDA 50-814

Subject: Approval of NDA 50-814 for Cayston in conjunction with 510 (k) clearance for the Altera[™] Nebulizer System.

As noted in the CDTL review dated February 10, 2010, there is substantial evidence of safety and effectiveness in the Cayston NDA 50-814 submission to recommend approval. Cayston is administered via inhalation by using the Altera nebulizer system. Gilead Sciences Inc. is the NDA holder for Cayston.

During the drug development process, the NDA applicant proposed, and the Agency agreed that separate applications for the drug Cayston and the Altera device could be submitted. Because the different timelines for completion of NDA reviews by CDER and completion of 510 (k) application reviews by CDRH, coordination between CDER and CDRH for concurrent action on the drug product and device was needed.

The review division completed labeling negotiations for NDA 50-814. Gilead Sciences Inc. submitted the agreed-upon labeling to the NDA on February 11, 2010. This labeling includes patient instructions for use of the Altera nebulizer and states: "CAYSTON is administered by inhalation using an Altera Nebulizer System. CAYSTON should not be administered with any other nebulizer."

Gilead Sciences Inc. also provided copies of draft labeling for the Altera nebulizer system for to CDER. I have reviewed the draft labeling for the Altera nebulizer. The information related to Cayston in the device labeling and instructions for "Taking a Treatment" are consistent with the labeling for the drug product. My only recommendation for revisions to the device labeling is in the section on taking a treatment (Section G, item 1). This item states:



This section should refer users to the Patient Instructions for Use for Cayston for instructions on how to mix (reconstitute) Cayston. This section should also tell patients not to put Cayston powder into the medication reservoir. I recommend that this section be revised as follows:

“Make sure the Handset is on a flat stable surface. See the Patient Instructions for Use for CAYSTON for instructions on how to mix (reconstitute) Cayston (aztreonam for inhalation solution). Pour only mixed Cayston liquid into the Medication Reservoir of the Altera Handset (Figure 13). Do not pour Cayston powder into the Medication Reservoir. Do not use other medications in the Altera Nebulizer Handset.”

CDRH should determine if the above revision is acceptable, and whether the remainder of the device labeling is acceptable from their perspective.

Because the drug product labeling contains information about the use of Cayston with the Altera nebulizer, the agreed-upon labeling for CAYSTON may not be considered adequate under 21 CFR 201.5 (f) if the Altera nebulizer is not also cleared.

Conclusions and Recommendations:

I recommend that CDER and CDRH work to take concurrent action on the NDA application for Cayston (NDA 50-814) and the 510 (k) application for the Altera Nebulizer System. If the 510 (k) application can not be approved within the time remaining for action on the NDA, then it may be appropriate to issue a complete response letter, noting the following deficiency:

Proposed labeling describes the method of administration for Cayston by use of an Altera nebulizer system; however, this device has not been cleared by the Center for Devices and Radiological Health.

I recommend that labeling for the Altera Nebulizer System be modified in section G (Taking A Treatment) item #1 to read as follows:

“Make sure the Handset is on a flat stable surface. See the Patient Instructions for Use for CAYSTON for instructions on how to mix (reconstitute) Cayston (aztreonam for inhalation solution). Pour only mixed Cayston liquid into the Medication Reservoir of the Altera Handset (Figure 13). Do not pour Cayston powder into the Medication Reservoir. Do not use other medications in the Altera Nebulizer Handset.”

CDRH should determine whether the device labeling is otherwise acceptable.

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

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/s/

JOHN J ALEXANDER
02/12/2010

Cross-Discipline Team Leader Memorandum NDA 50-814 Re-Submission

Date	February 10, 2010
From	John Alexander, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 50-814 (Re-submission dated August 12, 2009)
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 in cystic fibrosis (CF) patients with <i>Pseudomonas aeruginosa</i>
Recommended:	Approval

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 (CF). The NDA was submitted by Gilead Sciences, Inc. A complete response (CR) letter was issued to the applicant on September 16, 2008. The reader is referred to the CDTL memo dated September 2, 2008 (signed off September 15, 2008) for information about the original NDA review.

On August 12, 2009, a re-submission of NDA 50-814 was received. This memo focuses on the basis for the re-submission, the advisory committee discussion of the application, the reviewer findings for the re-submission, and the basis for the recommended action.

2. Background

Subsequent to the issuance of the complete response letter for NDA 50-814, the NDA applicant submitted a formal dispute resolution request to the Office of Antimicrobial Products on November 21, 2008. The main issue of contention in the request was whether the data from the two studies conducted by the applicant met “the evidentiary standard for regulatory approval”. The applicant contended that the two pivotal studies reviewed in the original NDA showed an overall favorable risk/benefit ratio, and that another study of the efficacy of aztreonam for inhalation solution (AI) was not needed. Specifically, the applicant contended that study CP-AI-005 still provided supportive evidence of efficacy despite the division’s concerns about the regimen effect in the trial. The dispute resolution went to a second level of appeal to the Office of New Drugs (OND) in a letter dated March 13, 2009. In a letter dated June 17, 2009, the appeal was

denied because the re-analyses of study CP-AI-005 that were conducted by the applicant constituted new data. The letter recommended that the applicant submit the re-analyses of study CP-AI-005 to the division as their response to the CR letter. The OND letter also recommended that the full application be presented to the Anti-Infective Drugs Advisory Committee. On August 12, 2009, the applicant submitted the re-analyses as part of the response to the CR letter.

3. CMC/Device

The CR letter of September 2008 included several deficiencies related to the methods for maintaining microbiological sterility of the final drug product. The CR letter listed additional information needed about solution (b) (4) sterilization/depyrogenation, media fill procedures and specifications at manufacturing sites. The CR letter also requested additional information about endotoxin testing for the aztreonam lysine product.

The Quality Microbiology review, dated November 4, 2009, by Dr. Vinayak Pawar was finalized on November 9, 2009. The review addresses all CMC deficiencies listed in the CR letter. The reviewer recommended approval from the microbiology product quality standpoint. At the time of this writing, the CMC review has not been finalized, though there were no deficiencies excepting those of the quality microbiology review in the original NDA. The CMC reviewer is working on review of carton/container labeling and the package insert. The office of compliance issued an overall recommendation of acceptable for NDA 50-814 facilities inspections on February 2, 2010.

The nebulizer to be used for delivery of AI is called the Altera nebulizer. The Altera nebulizer is based on a previously cleared general use nebulizer (the PARI e-flow). This device is the subject of a separate 510(k) supplement in CDRH to modify device labeling for specific use with CAYSTON (aztreonam for inhalation solution). At the time of this writing, it is unclear whether the device will be cleared at the same time as the approval action for the NDA is taken.

4. Nonclinical Pharmacology/Toxicology

There were no nonclinical pharmacology/toxicology (P/T) deficiencies in the original NDA and the P/T reviewer had no objections to product approval. The re-submission included reports for safety pharmacology studies in dogs and several genotoxicity studies. A P/T review by Dr. Amy Ellis, dated November 20, 2009, was archived on December 9, 2009. The reviewer again concluded that she had no objections to approval of the drug product. The additional genotoxicity information was the basis for a change in the reviewer's recommendations for product labeling. The changes were included in proposed labeling sent to the applicant.

5. Clinical Pharmacology/Biopharmaceutics

In the original NDA, the clinical pharmacology reviewer, Dr. Sarah Robertson, found the information submitted by the applicant to be acceptable. However, the reviewer noted that the proposed dose (75 mg TID) of AI may not be the most efficacious dose. The reviewer recommended that the applicant consider evaluation of a higher dose (150 mg) given twice daily, if additional clinical studies are conducted.

No new clinical pharmacology information was provided in the re-submission. A clinical pharmacology review of the re-submission by Dr. Yongheng Zhang was completed on January 22, 2010. The review provides the reviewer's perspective on the response to the CR letter, the advisory committee proceedings, and proposed labeling changes. The reviewer concluded that the applicant had provided an adequate response. However, the issue of whether an alternative dosing regimen would be more effective remains unresolved. The reviewer proposed phase 4 commitments to evaluate the regimen effect observed in study CP-AI-005 and to evaluate a higher dose regimen (>75 mg but ≤ 150 mg) given BID or TID. The recommendations of the clinical pharmacology reviewer were considered in the development of the phase 4 commitments described at the end of this memorandum.

6. Clinical Microbiology

The clinical microbiology review for the original NDA was conducted by Dr. Peter Coderre. In the original NDA review, he made no recommendation about the application approval. The treatment showed favorable effects on microbiological outcomes. Namely, patients in the treatment arm had lower or comparable loads of *Pseudomonas aeruginosa* in sputum, showed no increases in other CF pathogens, and had similar aztreonam susceptibility for *Pseudomonas aeruginosa* isolates at baseline and end of treatment. However, these microbiological outcomes did not correlate with clinical responses, so Dr. Coderre deferred to the clinical and statistical reviewers on the approval decision.

Dr. Coderre also reviewed the resubmission (review signature date – January 14, 2010). The re-submission did include new microbiology information as part of the final study report for the open-label follow-on study, CP-AI-006. The final report in the re-submission included more patients than had been included in the interim analysis submitted with the original NDA. The number of patients completing 9 cycles of AI treatment also increased. The clinical microbiology review of the resubmission summarizes the previous findings for the controlled trials, discusses the new data for CP-AI-006, provides the reviewer's perspective on the advisory committee discussion, and provides labeling recommendations. The reviewer recommended that AI be approved, and the labeling changes were included in the draft labeling sent to the applicant.

The review also notes the concern expressed by some advisory committee members about the potential for development of antibacterial resistance in *P. aeruginosa* isolates from CF patients. On this basis, the clinical microbiology reviewer recommended a phase 4

commitment studying *P. aeruginosa* susceptibility in CF patients. This recommendation was the basis for a post-marketing requirement discussed at the end of this memorandum.

7. Clinical/Statistical

The statistical reviewer for the original NDA, Dr. Christopher Kadoorie, completed a review of the resubmission, dated January 27, 2010. The clinical reviewer for the original NDA submission, Dr. M. Austin Imoisili, conducted a review of the additional safety information in the resubmission. Because Dr. Imoisili transferred to a different office within FDA, he limited his work on the resubmission to review of the new safety information.

7.1 Safety

The reader is referred to the medical officer's review (signed off on September 5, 2008) or the CDTL memo (signed off on September 15, 2008) for the original NDA submission for detailed safety findings from the controlled studies. Briefly, there were no significant safety findings that precluded approval of the drug product. In controlled studies, cough and fever were common adverse reactions that were reported at higher frequencies in AI patients than placebo patients. Many serious adverse reactions (AR) in controlled trials were related to pulmonary exacerbations, and cough and productive cough were the most commonly reported serious AR. There were no deaths in the controlled trials, but one death occurred during the follow-on study (CP-AI-006) in a patient with multiple hospitalizations related to hemoptysis. Hemoptysis occurred at similar rates in AI and placebo patients in the controlled trials.

In the resubmission, the main source of new safety information came from the completed study report for the follow-on study (CP-AI-006). This study enrolled patients from either of the controlled clinical studies (CP-AI-005 or CP-AI-007). Patients received AI or placebo BID in studies CP-AI-005 received AI 75 mg BID in this follow-on study. Patients who received AI or placebo TID in either controlled study received AI 75 mg TID in the follow-on study. In the original NDA, the interim report included 82 patients treated with AI BID and 125 patients treated with AI TID; in the final study report there were 85 AI BID patients and 189 AI TID patients. There was also a safety update including data from compassionate use programs (both US and international) and data from two ongoing trials.

The safety results from the final study report for study CP-AI-006 can be summarized as follows:

Deaths: There was one additional patient death in the final study report. This 57-year-old male patient with pre-existing renal disease received three courses of AI 75 mg TID. (In Study CP-AI-007, he was assigned to receive placebo.) He was hospitalized after the first course of AI treatment for pulmonary exacerbation, worsening chronic renal failure, and digital artery occlusion. He began hemodialysis during a second hospitalization. During a third hospitalization for digital artery occlusion (considered secondary to

caliciphylaxis), he decided to withdraw from hemodialysis and received palliative care. He withdrew from AI treatment at that time. He died about 6 weeks later from renal failure.

Serious Adverse Reactions: The only treatment-related serious AR reported in more than one patient in the follow-on study were cough, productive cough, and dyspnea exacerbated. Among all serious AR; cough, productive cough, dyspnea, and pulmonary function test decreased were reported more frequently (difference > 3%) in the AI TID than in AI BID patients. However, it is difficult to draw any conclusions regarding a dose-response relationship for these serious AR, because there were more AI TID patients, and the average number of cycles for the AI TID group was greater. The reported serious adverse reactions are similar to those reported as common AR in the controlled studies, and are typical symptoms known to occur in CF patients.

Discontinuations: There were 8 AI TID patients and 2 AI BID patients who discontinued for study drug intolerance or documented AR. Symptoms that led to discontinuation of treatment included decreased FEV1, chest discomfort, chest tightness, cough, and wheezing. These symptoms were reported in relation to drug treatment, and appear to represent drug-related bronchoconstriction. This was reported in no more than 2-4% of patients in either treatment group. Arthralgia, hemoptysis, and tinnitus were reported in one patient each among these discontinuations. The relationship of these single events to drug treatment is less clear.

Common Adverse Reactions: It is apparent from the common AR in the final study report that as multiple treatment courses were given, the number of AR increased substantially. For example, cough was reported in 87% of AI BID patients and 90% of AI TID patients. The following AR were reported more frequently in the TID group: productive cough, decreased appetite, dyspnea, nausea, sinus congestion, and asthenia. On the other hand, lung crackles and abdominal pain were more frequent in the AI BID group. Again, comparisons across these treatment groups should be made cautiously, since they are not randomized to these treatments. The types of AR reported did not appear to be different from the AR seen in controlled trials.

In his overall conclusions, the medical officer did not consider the reported AR to be different from the types seen in the initial NDA review. The medical officer did not consider the AR profile to constitute a barrier to product approval.

CDTL Safety Conclusions:

I concur with the conclusions of the medical officer. The analysis of safety in the comparative studies as part of the original NDA showed few common adverse reactions that were more frequent in AI patients compared to placebo. The most significant adverse reactions in the NDA database that could be ascribed to AI treatment are the occurrence of bronchospasm in roughly 3% of patients, and an apparent allergic reaction in one patient.

7.2 Efficacy

The reader is referred to the medical officer's review (signed off on September 5, 2008), the statistical review (signed off on July 22, 2008), or the CDTL memo (signed off on September 15, 2008) for efficacy findings from the original NDA submission. A brief description follows of the two controlled clinical trials performed as pivotal studies for the NDA application.

One study (CP-AI-007) was a placebo-controlled trial of 75 mg of AI given three times daily for 28 days to patients with CF with documented history of *P. aeruginosa* lung colonization, and baseline FEV₁ between 25% and 75% predicted. This study was designed to demonstrate the effect of treatment on pulmonary symptoms of CF at the end of a 28-day course of treatment. Pulmonary symptoms were measured using the respiratory domain of the cystic fibrosis questionnaire-revised (CFQ-R). Pulmonary function tests were performed in this trial as a secondary endpoint. These endpoints were also assessed at a follow-up visit 2 weeks after completion of study drug treatment. This study was successful in demonstrating improvement in respiratory symptoms for AI patients relative to placebo patients at the end of treatment. The treatment difference in the CFQ-R respiratory symptom domain between groups at day 28, the last day of treatment, was 9.7 points (95% CI: 4.31, 15.11). A difference of 10% between treatment groups (favoring AI) was also reported for FEV₁% predicted. The difference in pulmonary symptoms was still present, though smaller, at the follow-up visit [6.3 points – (95% CI: 1.22, 11.43)]; the difference in FEV₁% predicted (6%) was consistent with the changes in pulmonary symptoms. While the study showed a trend toward decreased hospitalization and anti-pseudomonal antibacterial use, the results were not statistically significant for these endpoints.

The second study (CP-AI-005) was more complex. This study enrolled CF patients ≥ 6 years of age with FEV₁ 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 placebo BID or TID. Patients were randomized in a 2:2:1:1 ratio to these groups, respectively. The trial had a longer follow-up period than the other study, because the goal was to evaluate exacerbations after treatment.

The applicant claimed success on the primary endpoint comparing time to exacerbation in pooled AI versus pooled placebo groups. However, the regimen effect favoring BID over TID in both the AI and placebo groups led reviewers to conclude that the effect on time to exacerbation are not reliable. Regardless of the reliability of the primary endpoint results, the applicant could not show that the time to exacerbation differed between AI TID (the to-be-marketed dose) and pooled placebo. The statistical review of the resubmission highlights the lack of evidence for a treatment effect on time to exacerbation. This conclusion was not altered by the re-analyses provided by the

applicant in the re-submission. The CDTL agrees with this conclusion.

(b) (4)

The secondary outcomes results for study CP-AI-005 included evaluation of CFQ-R at the end of treatment and change in FEV₁% predicted; though it should be noted that the treatment with TOBI for 28 days prior to treatment with study drug may have affected the ability to see a difference in respiratory symptoms between AI and placebo treatment groups. In this study, the treatment difference in CFQ-R at the end of 28 days of treatment with pooled AI or pooled placebo was 5.01 points (95% CI: 0.81, 9.21). For the comparison of AI TID and pooled placebo the treatment difference was 4.4 points (95% CI: -0.94, 9.69). Change in FEV₁% predicted was also significant for both the pooled AI to pooled placebo comparison (median difference 2.5%; 95% CI = 0.721, 4.409) and the AI TID to pooled placebo comparison (median difference 2.4%; 95% CI= 0.117, 4.561).

As was noted in the background section, the NDA re-submission included re-analyses of the study 005 data. The new analyses attempted to account for the primary endpoint findings by investigating the effect of change in FEV₁ as a covariate. In essence, the applicant argued that the reason why a greater number of patients receiving AI TID had exacerbations more frequently than patients in the placebo BID group because greater declines in FEV₁ after completion of study drug treatment in the AI TID group caused investigators to initiate treatment of pulmonary exacerbations in the AI TID patients. In the statistical review of the re-submission, the reviewer considered the re-analyses inadequate for several reasons. The reviewer raised concerns about the post-hoc nature of the analyses; the reviewer considered the evidence from the re-analyses weak because of uncertainty related to the regimen effects and the missing data; the reviewer questioned the methods for imputing change in slope of FEV₁, since FEV₁ varies over time; and the reviewer also noted the potential for serious biases when using FEV₁ slope as a covariate because it is affected by drug treatment. Lastly, one of the sensitivity analyses relies on changing patient classification from ‘event’ to ‘no event’ based on lack of no decline in FEV₁, but this change in classification is inappropriate if patient symptoms in the absence of FEV₁ decline were the reason for treatment. For these reasons, the statistical reviewer considered the re-analyses as inadequate for explanation of the primary analysis findings for study 005.

(CDTL Comment: I agree with the statistical reviewer’s findings for the re-analysis. It does not provide adequate explanation for the unusual findings in the study 005 primary analysis. While decline in pulmonary function after treatment in the AI TID group might contribute to greater numbers of patients in this arm receiving treatment for a pulmonary exacerbation, it does not explain the reasons for differences between the two placebo groups. The methods for determining change in FEV₁ slope are questionable, since there is variability in FEV₁ measurements.)

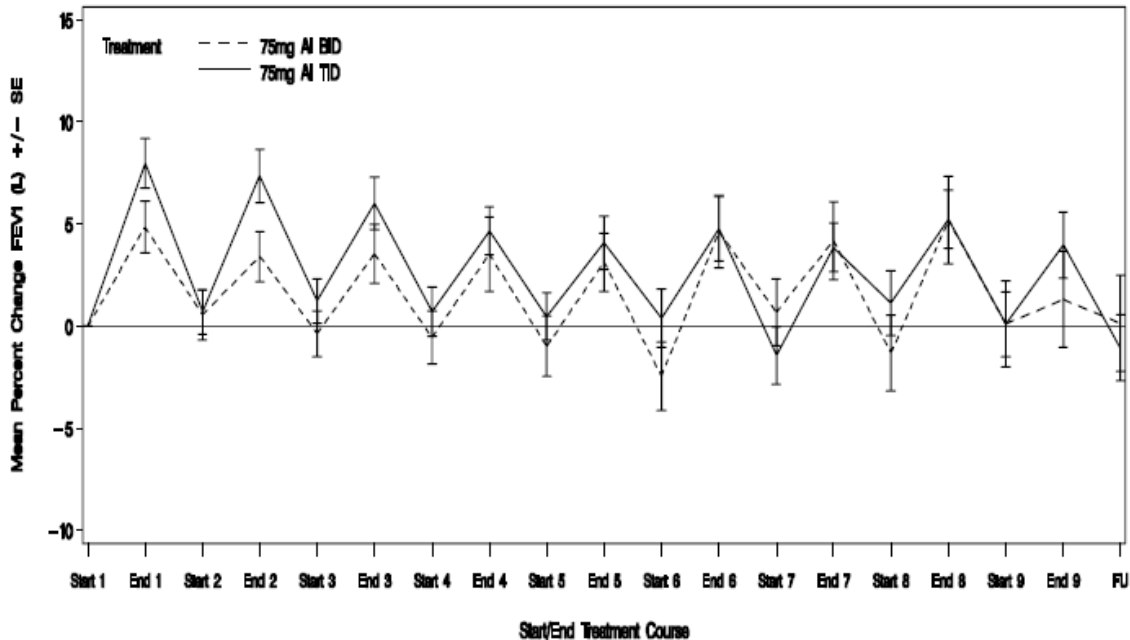
In the statistical review of the re-submission, the reviewer concludes that the submission “fails to provide adequate evidence of reduced pulmonary exacerbation in CF patients”, though it did provide “some evidence of an improvement in respiratory symptoms from Day 0 to Day 28 from Study 007”. The statistical reviewer’s main concerns with the study 007 results are the smaller change in CFQ-R for adult patients at Day 28 and the

decline in treatment effect at Day 42. The statistical review also states that “Due to the nature of Cystic Fibrosis due to *P. aeruginosa*, clinical and other considerations should also be taken into account when evaluating the evidence of improvement in respiratory symptoms”. The reviewer still recommends additional trials be conducted “to better address many of the limitations stated” in the review.

(CDTL Comment: In discussions with the statistical team, the above conclusions were made in recognition of the Anti-Infective Drugs Advisory Committee (AIDAC) recommendations, discussed in the next section of this memorandum, allowing the clinical reviewers and Division/Office supervisors leeway to consider the evidence of effect on respiratory symptoms, the serious nature of cystic fibrosis, the need for additional treatments in this population, and the overall public health benefits and risks. The statistical reviewer’s recommendations differ from his original NDA review where he stated that there was a “lack of substantial evidence” and recommended that an additional study be conducted to demonstrate efficacy and safety.)

One additional consideration is the efficacy results of the open-label follow-on trial, study CP-AI-006. In this study, there were two groups of patients; those who received AI or placebo BID from study CP-AI-005 (n=85), and those who received AI or placebo TID from either study CP-AI-005 or CP-AI-007 (n=189). The following graphs from the final study report show the changes in FEV₁ and CFQ-R respiratory domain for the AI BID and AI TID treatment groups in this follow-on study.

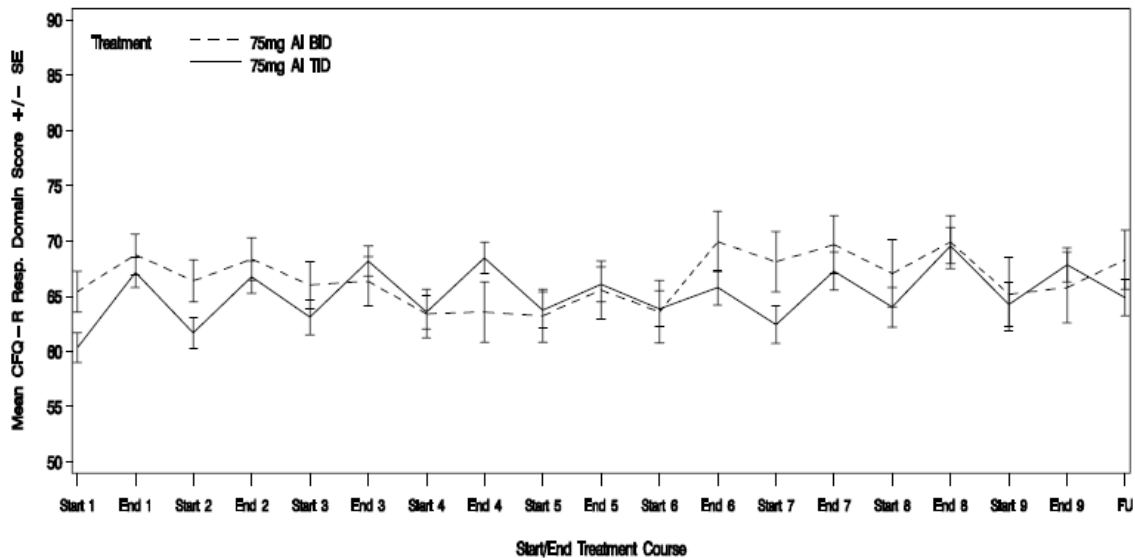
Figure 1: Mean % Change in FEV₁ (L) by Treatment Group over Multiple Visits in CP-AI-006



These figures are provided because the AIDAC were shown the above figure by the NDA applicant. Several AIDAC members considered the changes in FEV₁ with treatment as

supportive of the AI treatment effect in study CP-AI-007. The applicant suggested that the comparison of AI BID and AI TID treatment responses in this graph was suggestive of better response to AI TID treatment. However, the following graph of changes in CFQ-R respiratory domain scores over multiple treatment cycles shows significant variance in the CFQ-R endpoint. As noted with the safety information, any comparisons of results for these non-randomized groups should be made cautiously. At best, these results can be taken to show that both CFQ-R respiratory domain scores and FEV₁ increase with treatment, though the changes in CFQ-R respiratory domain score are inconsistent.

Figure 2: CFQ-R Respiratory Domain Scores by Treatment Group over Multiple Visits in CP-AI-006



CDTL Efficacy Conclusions:

There is substantial evidence of the efficacy of aztreonam for inhalation (AI) solution, but only for the claim of improvement in respiratory symptoms. The responses on the CFQ-R respiratory domain appear to show an effect on respiratory symptoms that are meaningful to patients; though there are some concerns about the qualitative work done to develop the CFQ-R (see discussion in section 9 of this memorandum). Limited supportive evidence for this effect on respiratory symptoms comes from studies CP-AI-005 and from the open-label follow-on study CP-AI-006. There is not sufficient evidence for the effect of AI solution on delaying time to exacerbation. The regimen effect seen in study CP-AI-005 does not allow meaningful conclusions about the effect of AI treatment on subsequent exacerbations. There is also some regimen effect on the CFQ-R results, based on higher mean CFQ-R responses at day 28 for the AI BID than the AI TID group; however, there is no apparent difference in responses on the CFQ-R for patients in the placebo BID and placebo TID groups. Therefore, the CFQ-R results for the effect of pooled AI versus pooled placebo and the similar trend for AI TID versus pooled placebo can be taken as limited supportive evidence for the study CP-AI-007 results. I agree with

the recommendations of the statistical and clinical reviewers that an additional study is needed to determine whether the regimen effect seen in study CP-AI-005 can be replicated; the additional trial can be conducted as a post-marketing commitment.

8. Advisory Committee

On December 10, 2009, the Anti-Infective Drugs Advisory Committee (AIDAC) met to discuss the NDA 50-814 submission for Cayston (aztreonam for inhalation solution). The meeting included presentations by the applicant and the FDA reviewers of the efficacy and safety results from the clinical trials. The applicant presented their perspective of the safety and efficacy of AI from the controlled trials and the open-label follow-on study. The FDA presentations included:

- A presentation on study CP-AI-007 results and safety information from the clinical trials by the CDTL, Dr. John Alexander;
- A presentation on study CP-AI-005 results by Dr. Christopher Kadoorie;
- A presentation about dose selection by Dr. Sarah Robertson.

The CDTL presentation discussed the drug development program for AI, the drug safety information, the favorable results of study CP-AI-007, and some limitations of the questionnaire used in the trials. The FDA presentation by Dr. Kadoorie described the reviewer's concerns about the outcomes in study CP-AI-005, including the regimen effect and the re-analyses of the results provided by the applicant in the re-submission. Dr. Robertson discussed how the dose regimen used in the pivotal trials was selected, and she raised questions about whether alternative BID regimens may provide better outcomes.

There were three presenters at the open public hearing, Dr. Bruce Marshall of the CF Foundation, Dr. Patrick Flume of the Medical University of South Carolina, and Ms. Beth Sufian (a CF patient and director of the CF Legal Information Hotline). All open public hearing speakers emphasized the unmet medical need for additional inhaled antibacterials in CF patients, and advocated for the approval of AI. The open public hearing was followed by some discussion of the clinical trial results by the committee. The committee was asked to vote on two questions:

1. Has the Applicant provided substantial evidence of the efficacy and safety of 75 mg three times daily of AZLI for the requested indication of improvement of respiratory symptoms and pulmonary function in cystic fibrosis patients with *Pseudomonas aeruginosa*? In your response, discuss the rationale for your answer.
 - a. If you voted YES, are there any specific issues that should be addressed in labeling?
 - b. If you voted NO, what additional information is necessary?

The committee vote was Yes – 15 and No – 2. All of the clinicians and one of two statisticians on the committee voted that substantial evidence of safety and effectiveness had been demonstrated. One of the two no votes came from Dr. Shyr, a statistician who

based his no vote on inadequate evidence of efficacy from study CP-AI-005, though he also noted some limitations in the degree of difference in symptoms measured by the CFQ-R in study CP-AI-007. The second no vote came from Ms. Young, a patient representative on the committee, who voted against approval because she didn't think the effectiveness of the drug was proven. She also expressed concerns about the development of aztreonam resistance. Among the committee members voting yes, many cited the unmet medical need for inhaled antibacterials in CF patients. Many of the yes voters viewed the benefit/risk for AI to be favorable, because of the absence of a safety signal and a treatment effect, though modest, was present. Some of the committee members noted the risk for development of aztreonam resistance in these patients as a problem that should be tracked after approval.

2. Has the applicant identified the correct dose and regimen for AZLI for the requested indication? In your response, discuss the rationale for your answer and discuss if there is any additional information that should be generated regarding the dose and regimen.

All 17 committee members voted yes, though they modified the question by asking whether a correct dose and regimen has been identified. The consensus of the committee members appeared to be that a favorable benefit/risk had been demonstrated for the 75 mg TID dose regimen. Some committee members noted that the optimal dose regimen is not necessarily identified in clinical studies, and recommended further exploration of BID dose regimens. However, some committee members emphasized that approval should not be delayed by additional studies of drug dosing. Others expressed reservations relating to the activity of aztreonam (time above MIC) being counter to the proposed regimen change, and the difficulty in conducting studies of different dose regimens.

9. Other Relevant Regulatory Issues

An important aspect of the AI development program was the use of a patient-reported outcome measure, the respiratory domain of the cystic fibrosis questionnaire-revised (CFQ-R). The evaluation of the NDA included consultation to the Study Endpoints and Labeling Development (SEALD). SEALD also provided consultation during the drug development process under the IND. However, the use of the respiratory domain of the CFQ-R was permitted several years before the availability of current Guidance on the development of PRO measures. The main focus during product development was on interpretation of changes in the existing CFQ-R respiratory domain, rather than the qualitative development of the PRO measure. As a consequence, there are limitations to the clinical understanding of the reported treatment difference in clinical trials. The consultation review by Dr. Elektra Papadopoulos, dated February 1, 2010, and her prior consultation review in the original NDA point out some of these limitations.

(CDTL Comment: If judged against recommendations for development of PRO measures in current Guidance, the respiratory domain of the CFQ-R has significant deficiencies. However, the tool does ask questions about symptoms (mainly cough, sputum production

and wheezing) that are important to patients with CF. Overall, the clinical trial results using the CFQ-R respiratory domain do provide us with information about improvement in these symptoms. However, the 2-week recall period used in the questions, and the missing qualitative information (such as the patient's interpretation of "trouble breathing" and whether all important respiratory symptoms are captured in the CFQ-R) should limit the use of the CFQ-R in future trials.)

10. Financial Disclosure

Since no new studies were included in the re-submission, there was no new information about financial disclosures presented for review. To obtain information related to financial disclosure for AI clinical studies, the reader is referred to the CDTL review memo for the original NDA.

11. Labeling

Labeling recommendations for carton and container labeling were sent to the applicant in a discipline review letter dated December 17, 2009. The labeling recommendations from all reviewers were collected in draft proposed labeling and sent to the applicant on January 25, 2010. At the time of this writing, the sponsor has provided revised carton and container labeling for review. A revised package insert was provided by the applicant on February 1, 2010. Further revisions to the package insert and the patient labeling were sent to the applicant on February 5, 2010. Official submission of labeling to the NDA is still pending, though there is agreement on the labeling content.

12. DSI Audits

There were no concerning findings in the clinical inspection summary for the original NDA. Since no new clinical studies were included in the re-submission, there were no new clinical inspections requested of the Division of Scientific Investigations (DSI).

On January 28, 2010, DSI issued a warning letter (Official Action Indicated) to Dr. Samya Nasr of Ann Arbor, MI that was related to this investigator's participation in study CP-AI-005 and CP-AI-007, as well as other studies for unrelated drug products. Based on the DSI inspection findings, DSI recommended that DAIOP not rely on the data generated at this investigator's site for study CP-AI-005. This investigator contributed very few patients to either of the controlled clinical studies in the NDA for AI. Exclusion of the patients from this investigator site for study CP-AI-005 did not appreciably alter the study results.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of NDA 50-814 for Cayston (aztreonam for inhalation solution).

- Risk Benefit Assessment

The applicant has provided substantial evidence of a treatment effect of AI on improving respiratory symptoms in patients with CF. This evidence comes mainly from the successful trial, CP-AI-007, with limited supportive evidence coming from study CP-AI-005 and the open-label follow-on study. These benefits outweigh the risks from minor adverse reactions seen more frequently in AI-treated patients in the comparative clinical trials. The most significant risks of AI identified in the NDA application are bronchospasm and allergic reactions.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None: standard methods for evaluation of post-marketing adverse reactions are sufficient.

- Recommendation for other Postmarketing Requirements and Commitments

I concur with the recommendations of the clinical microbiology reviewer for monitoring antibacterial resistance to aztreonam in isolates of *Pseudomonas aeruginosa* from patients with CF. Because of the significant public health consequences of antibacterial resistance in *P. aeruginosa*, this study should be a post-marketing requirement. On January 18, 2010, the NDA applicant submitted a letter agreeing to conduct the following study.

1. Conduct a prospective study in the United States over a five year period after introduction of Cayston (aztreonam for inhalation) to the market to determine if decreased susceptibility to aztreonam is increasing in *Pseudomonas aeruginosa* from cystic fibrosis (CF) patients. Provide a detailed study protocol to the Agency for review and comment before commencing the study. Interim reports of changes in *P. aeruginosa* susceptibility from CF patients should be submitted annually for five years. After the first year, the report should be cumulative.

Final Protocol Submission: by 07/2010

Study Start Date: by 04/2011

First Interim Report: by 01/2013, then annually

Study Completion Date: by 04/2017

Final Report Submission: by 01/2018

In addition, the NDA applicant agreed to conduct the clinical trials listed below. The first of these trials is an ongoing study comparing treatment with the proposed product to treatment with tobramycin solution for inhalation. This trial will provide some information on the comparative effectiveness of the proposed product and the only antibacterial for inhalation approved in the US. The second of these trials is intended to address the questions of whether the regimen effect seen in study CP-AI-005 can be replicated in another trial. This trial could potentially address the clinical pharmacology questions of whether a higher dose of AI would be more effective than the approved dose, but inclusion of higher doses could complicate interpretation of results. The main purpose of the trial is to address whether some currently unknown factors would result in better outcomes for patients receiving AI treatment BID rather than TID.

2. Conduct a prospective, randomized trial evaluating the safety and efficacy of Cayston versus TOBI[®] (tobramycin solution for inhalation) in the treatment of patients with cystic fibrosis. Enrolled patients should receive 75 mg of aztreonam for inhalation three times daily or 300 mg of tobramycin solution for inhalation twice daily in 28-day treatment cycles over a trial period of 24 weeks. The trial should enroll CF patients \geq 6 years of age with history of *Pseudomonas aeruginosa* on sputum culture.

Final Protocol Submission: 13 April 2009

Trial Start Date: Initiated Protocol GS-US-205-0110 in 2008 in the European Union; fully enrolled in 2009

Trial Completion Date: by 05/2010 (last patient last visit for the randomized portion of the study)

Final Report Submission: by 09/2010

3. Conduct a prospective trial comparing twice daily and three times daily administration of Cayston to evaluate the presence or absence of a regimen effect. The trial should enroll CF patients \geq 6 years of age with history of *Pseudomonas aeruginosa* on sputum culture.

Final Protocol Submission: by 07/2010

Trial Start Date: by 04/2011

Trial Completion Date: by 04/2013

Final Report Submission: by 01/2014

- Recommended Comments to Applicant

None

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J ALEXANDER
02/10/2010