CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50-753

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	Included	Pending Completion	Not Prepared	Not Required
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Chemistry Review(s)	X			
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Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)			X	
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Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-753

Trade Name: TOBI

Generic: (tobramycin solution for inhalation)

Sponsor: PathoGenesis Corporation

Approval Date: December 22, 1997

Indication: Provides for the management of cystic fibrosis patients with Pseudomonas aeruginosa

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 50-753

APPROVAL LETTER

NDA 50-753

PathoGenesis Corporation
Attention: Bill Pitlick, Ph.D.
Director, Regulatory Affairs
201 Elliott Avenue West
Seattle, WA 98119

DEC 22 1997

Dear Dr. Pitlick:

Please refer to your new drug application dated July 10, 1997, received July 10, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TOBI™ (tobramycin solution for inhalation). We note that these products are subject to the exception provisions of Section 125 (2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your pre-submissions dated March 20, March 21, April 9, April 21, April 30, May 13, June 19, and June 20, 1997. We also acknowledge receipt of your submissions dated July 21, August 1, August 6, August 7, August 25, August 27, August 28, September 15, September 19, October 9, October 10, October 15, October 16, October 17, October 20, October 21, October 24, October 27, November 4, November 25, December 3, and December 22, 1997. The User Fee goal date for this application is January 9, 1998.

This new drug application provides for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-753. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated December 22, 1997. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 50-753
HFD-520/Div. files
HFD-520/CSO/B. Duvall-Miller
HFD-520/MO/J. Alexander
HFD-590/MO/M. Mann
HFD-520/SMO/J. Soreth
HFD-520/Chem/S. Pagay 12/22/97
HFD-520/TLChem/D. Katague
HFD-520/Micro/J. King
HFD-520/TLMicro/A. Sheldon 12/22/97
HFD-520/Pharm/A. Ellis 12/22/97
HFD-520/TLPharm/R. Osterberg
HFD-725/Stats/T. Hammerstrom
HFD-725/TLStats/D. Lin 12/22/97
HFD-880/BioPharm/J. Zheng 12/24/97
HFD-880/TLBioPharm/F. Pelsor
HF-35/CSO/E. McNeily
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC/J. Spearmon (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Concurrence only:
HFD-520/SCSO/J. Bona 12/22/97
HFD-520/MO/J. Alexander JA 12/22/97
HFD-520/SMO/J. Soreth
HFD-520/ActDivDir/G. Chikami 12/22/97

Drafted by: bdm/December 15, 1997/A:\50753.WPD
Initialed by:
final: BDM 12/22/97

APPROVAL (AP) [with Phase 4 Commitments]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-753

MEDICAL REVIEW(S)

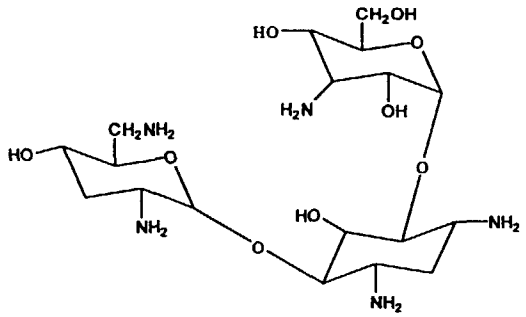
MEDICAL OFFICER REVIEW OF NDA 50,753

Date of Submission: July 10, 1997
CDER Stamp Date: July 11, 1997
Date Received by Reviewer: July 11, 1997
Date Review Completed: Dec. 22, 1997
Date Review Written: June 19, 1998

Applicant: PathoGenesis Corporation
201 Elliott Ave. West, Suite 150
Seattle, WA. 98119
Regulatory Contact: William H. Pitlick, Ph.D.
(206)467-8100

DRUG PRODUCT INFORMATION

Generic Name: Tobramycin solution for inhalation
Trade Name: TOBI™
Chemical Name: O-3-amino-deoxy-α-D-glucopyranosyl-(1->4)-O-[2,6 diamino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl-(1->6)]-2-deoxy-L-streptamine
Chem. formula: $C_{18}H_{37}N_5O_9$
Mol. weight: 467.52.
Chem. structure:



Drug Category: Aminoglycoside antibiotic
Dosage Form: 60 mg/mL tobramycin solution in 5 mL ampules
Route of Administration:
Inhalation via Pari LC+ jet nebulizer

PROPOSED INDICATIONS AND USAGE

The sponsor is seeking a single indication for use in cystic fibrosis patients. The proposed wording is as follows:

Redacted 1

pages of trade secret and/or confidential commercial information

REGULATORY BACKGROUND

Related Drugs:

Studies by the sponsor were carried out under IND Preliminary work was also done by under an investigator IND . The active ingredient, tobramycin sulfate, is identical to the active ingredient in the currently marketed intravenous formulation of tobramycin.

Materials Reviewed:

The sponsor submitted 23 volumes under the original NDA dated July 10, 1997. In addition, there were two early submissions made to the NDA which included clinical study material on the pivotal trials. The first submission was dated April 21, 1997 and included 14 volumes. This submission also included a CD-ROM which contained scanned copies of the case report forms in .PDF format. The second early submission was dated May 13, 1997 and included 15 volumes.

CHEMISTRY MANUFACTURING CONTROLS

Please refer to the review of chemistry, manufacturing, and controls by Shrikant N. Pagay, Ph.D., for the complete review. This discussion will be limited to a few comments pertinent to the clinical use of this product.

As noted above, this drug product does not represent a new chemical entity, but is a new formulation of tobramycin prepared for inhalation. The drug substance is produced in bulk at two facilities. They are located in the People's Republic of China and Hungary. Production of tobramycin solution and packaging occurs at Automated Liquid Packaging, Inc. in Woodstock, Il. Bulk solution is prepared so that 5 mL of solution contains 300 mg of tobramycin, 11.25 mg of NaCl, and small amounts of Sulfuric acid and Sodium Hydroxide, used for pH adjustment. The small amount of NaCl maintains a hypo-osmotic solution. The final solution is equivalent to mOsm/Kg water. Nitrogen is used in packaging as an anti-oxidant. filling of ampules employs

Six ampules are sealed in a laminated foil overpouch. Final packaging of the drug product is completed at Packaging Coordinators, Inc. in Philadelphia, Pa.

It is important to note that the formulation does not contain any preservatives. The sponsor most likely will use this statement in advertising. However, stability of the final drug product must be well defined, since the product is intended for long-term use.

ANIMAL PHARMACOLOGY/TOXICOLOGY

Please refer to the Pharm/Tox review by Amy Ellis, Ph.D., for the complete review. The complete list of nonclinical studies is provided in that review. It should be noted that provided the sponsor with some nonclinical toxicity study reports, but PathoGenesis Co. was not given permission to cross reference the IND . The only limitation to the nonclinical toxicology data provided is that the carcinogenic potential of chronic aerosol administration was not investigated. The pharmacologist recommended approval of the NDA, provided that the sponsor submit data from a two year carcinogenicity study in rats receiving tobramycin administered via inhalation. The protocol for a two year bioassay was acceptable to the CDER Executive Carcinogenicity Assessment Committee, and the study is in progress.

MICROBIOLOGY

Please refer to the Microbiology review by James King, Ph.D., for the complete review. The conclusions of the microbiologist recommended approval of this application with the statement that "Tobramycin has *in vitro* activity against a wide range of gram-negative organisms including *Pseudomonas aeruginosa*." The pathogen *Burkholderia cepacia* was not discussed in the review. Cystic fibrosis patients with this organism were excluded from clinical studies. This organism will be discussed later in this review. The issue of susceptibility breakpoints will also be discussed briefly in the results of the pivotal trials. The microbiologist's conclusions included a statement that the susceptibility breakpoints for parenteral tobramycin do not apply to TOBI.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

Please refer to the Biopharmacology review by Jenny Zheng, Ph.D., for the complete review. Since this product is intended for inhalation, the goals in its development were to achieve high local concentrations of tobramycin in the sputum, and provide limited systemic exposure. Review of pharmacokinetic(pk) data from the pivotal trials concluded that high sputum tobramycin concentrations are achieved, but that the variability is high. The systemic exposure to tobramycin was low based on serum levels measured one hour after TOBI administration. The reviewer concluded that the human pharmacokinetics section of the NDA was acceptable. The reviewer noted that the population pk analysis lacked solid foundation, and recommended deletion of statements regarding The sponsor agreed to these changes in negotiation of the label.

HUMAN CLINICAL EXPERIENCE

This review will discuss the results of the clinical trials performed by PathoGenesis Corporation. The trials conducted by the sponsor are listed below:

PC-TNDS-001: A Phase II Clinical Trial to Compare Safety, Efficacy and Pharmacokinetics of an Aminoglycoside (Tobramycin) Formulation Administered by Three Different Nebulizer Delivery Systems to Patients with Cystic Fibrosis.

PC-TNDS-002: A Phase III Placebo Controlled Clinical Trial to Study the Safety and Efficacy of Tobramycin for Inhalation in Patients with Cystic Fibrosis (CF).

PC-TNDS-003: A Phase III Placebo Controlled Clinical Trial to Study the Safety and Efficacy of Tobramycin for Inhalation in Patients with Cystic Fibrosis (CF).

PC-TNDS-004: An Open-Label Follow-On Trial of Tobramycin for Inhalation in Patients with Cystic Fibrosis

PC-TNDS-007: An Open-Label Follow-On Trial of Tobramycin for Inhalation in Patients with Cystic Fibrosis

PC-TNDS-001 is a pharmacokinetic study in which each subject would receive no more than 3 doses of aerosolized tobramycin. A summary of the safety and pharmacokinetics results are in the following section. This largest part of this discussion will focus on PC-TNDS-002 and -003, the pivotal phase III trials for this submission. Two open-label follow-on trials, PC-TNDS-004 and PC-TNDS-007, were each designed as six month trials. Patients who completed either PC-TNDS-002 or -003 could enroll in PC-TNDS-004. Subjects who completed this six month follow-on trial could enroll in PC-TNDS-007.

In PC-TNDS-004, seventy patients had either completed the trial or withdrawn. These seventy patients were included in an interim report. Results for PC-TNDS-007 were not available at the time of submission. This trial will not be discussed further in this review.

PC-TNDS-001
"A Phase II Clinical Trial to Compare Safety, Efficacy and Pharmacokinetics of an Aminoglycoside (Tobramycin) Formulation Administered by Three Different Nebulizer Delivery Systems to Patients with Cystic Fibrosis"
(M.O. Comment: This is a pharmacokinetic study which monitors the safety of administration of a single dose of aerosolized tobramycin. Efficacy was not part of the trial.)

Objectives: To determine
1) which of the three nebulizer systems could aerosolize sufficient tobramycin sulfate to achieve a sputum tobramycin concentration of µg/g or greater in at least % of the patients measured minutes after completion of dose administration;
2) whether a tobramycin delivery system that achieved a sputum concentration of µg/g or greater was safe and well-tolerated by patients.

Procedure: This was an open label, randomized, cross-over, three arm study in ten centers. Sixty-eight patients with cystic fibrosis(CF) were randomized using a "stratified, permuted block randomization scheme" into three nebulizer groups. The inclusion and exclusion criteria for this trial are shown below:

Inclusion Criteria
1. Informed consent obtained.
2. ≥8 years of age.
3. Documented sweat chloride ≥60 meq/L by quantitative pilocarpine iontophoresis test (QPIT) or homozygosity for ΔF508 mutation and two clinical findings consistent with cystic fibrosis.
4. Ability to expectorate ≥2 gm sputum in a 24 hr period.
5. FEV_1 30% predicted and oxygen hemoglobin saturation ≥90% at rest in room air.

(M.O. Comment: The age group for this study is just slightly older than for the pivotal trials (≥ 6 yrs). The FEV1 requirement is also slightly higher. However, these inclusion criteria are close enough to the target population in the phase III trials.)

Exclusion Criteria
1. Administration of inhaled or intravenous aminoglycosides within seven days prior to initial study drug administration.
2. Administration of inhaled rhDNase within 48 hours prior to study drug administration.
3. Administration of any investigational drug within seven days of study initiation.

4. Positive urine pregnancy test.
5. Hemoptysis ≥30 cc at any time within 30 days prior to study initiation.
6. Known hypersensitivity to aminoglycosides.

(M.O. Comment: The reasons for limitations on inhaled rhDNase are unclear. It is possible that the sponsor felt some adverse reaction possible with the combination. For the purposes of this pharmacokinetic study, this limitation is acceptable.)

Only 61 patients were evaluated on all three nebulizer systems. Equal numbers of males and females were divided into the three groups. The arms consisted of the following:

1. UltraNeb (Previously used delivery system in Ramsey et al study): Ultrasonic DeVilbiss UltraNeb 99 or UltraNeb 100 ultrasonic nebulizer using a 30-mL solution of ½ Normal Saline (NS) containing 20 mg/mL tobramycin. Inhalation proceeded for 200 inspirations. **(M.O. Comment: The UltraNeb 99 and 100 were considered equivalent systems by the sponsor. The solution used for nebulization in the ultrasonic nebulizers differs in concentration from the formulation used in the jet nebulizers or the phase III trials. This trial was carried out to test the feasibility of delivering the drug product with a jet nebulizer. As a result, we do not have information on the pharmacokinetics of the final drug product when used in an ultrasonic nebulizer.)**

2. Sidestream: Sidestream jet nebulizer with Pulmo-Aide® compressor using a 5-mL solution of 1/4 NS containing 60 mg/mL tobramycin. Inhalation proceeded until sputtering of the nebulizer.

3. Pari LC: Pari LC jet nebulizer with Pulmo-Aide® compressor using a 5-mL solution of 1/4 NS containing 60 mg/mL tobramycin. Inhalation proceeded until sputtering of the nebulizer.

Each patient received in random order one administration from each nebulizer delivery system. A Pulmo-aide compressor was used with each nebulizer to deliver compressed air at 8 L/min. Two different formulations of tobramycin were used. The jet nebulizers used 300 mg of tobramycin in 5 mL of 0.25 normal saline(NS). Treatment was continued until the nebulizer sputtered. For the ultrasonic nebulizer, 30 mL of a 20 mg/mL tobramycin solution in 0.5 NS was used. The patients were given 200 inhalations from the ultrasonic nebulizer. Additional tobramycin solution was added to the nebulizer if the amount was

insufficient to deliver 200 inhalations. Four patients required 600-900 mg of tobramycin, and nine patients required 600-1200 mg of tobramycin.

Patients had baseline physical examination, spirometry, and sputum and serum samples for tobramycin. Patients received tobramycin by each of the aerosol delivery systems. Aerosol duration, number of inhalations, and signs of respiratory distress were monitored. Patients rinsed and gargled with normal saline three times following completion of aerosol therapy. Sputum specimens were collected approximately 10 minutes after rinsing, and 1 and 2 hours after completion of aerosol drug administration. Serum samples were obtained 1 and 2 hours after treatment. Airway irritation and acute bronchospasm were assessed by spirometry immediately prior to administration and 30 minutes post-completion. Administration by each nebulizer was separated by at least 48 hour.

Results: The pharmacokinetic data obtained from this trial were reviewed in the previous section on human pharmacokinetics. The efficacy evaluable population consisted of 32 males and 29 females. The mean age of 21.4 is similar to the mean age for patients in the pivotal trials. All three nebulizer systems achieved the objective of producing a tobramycin concentration of µg/g or greater in at least % of the patients. It should be noted that "statistical significance was achieved only by the UltraNeb using the minute sputum values and for both the UltraNeb and Sidestream using the maximum sputum values". **(M.O. comment: Testing for proportion of subjects with maximum sputum concentration µg/g)** The following table shows the number(%) of patients with peak sputum tobramycin concentration (measured at 10 min, 1 hour, or 2 hours after completion of aerosol administration) above µg/g.

N(%) of patients with max sputum concentration µg/g

	Ultraneb	Sidestream	Pari LC
µg/g	3(5%)	4(7%)	8(13%)
µg/g	58(95%)	57(93%)	53(87%)

(M.O. Comment: Although the proportion of patients achieving the target sputum concentration was lower for the Pari LC than for the other nebulizers, the Pari LC produced higher mean and median sputum concentrations than the Sidestream jet nebulizer. The Ultraneb produced both greater mean sputum concentrations as well as higher proportions of patients achieving target sputum

concentration. However the goal of this trial seemed to be to assure the sponsor that jet nebulizers could produce results close to the ultrasonic nebulizer, which is more expensive and cumbersome.)

Safety analysis for this and the other studies in this review was completed in a separate review. Please see the review by Marianne Mann, M.D. for details. What follows is a group of tables that show the adverse events reported in this trial. It should be noted that many of the reported adverse events are likely related to underlying CF.

Summary Listing of Individual, Drug-Related Adverse Events

Delivery System	Adverse Event	Body System	Relation-ship	Severity	Frequency
UltraNeb	Abdominal Pain	Abdomen	Remote	Mild	1
	Bronchospasm	Lungs	Probable	Moderate	1
	Fever	Misc.	Remote	Mild	1
	Few Scattered Petechia	Skin	Remote	Mild	1
	Hemoptysis	Lungs	Possible	Mild	1
	Nausea	Abdomen	Remote	Mild	2
	Runny Nose	HEENT	Remote	Mild	1
	Sore Throat	Misc.	Remote	Mild	1
	Vomiting	Misc.	Remote	Mild	2
Sidestream	Bronchospasm	Lungs	Possible	Mild	1
	Cough	Lungs	Remote	Mild	1
	Cough	Lungs	Possible	Moderate	1
	Fatigue	Misc.	Possible	Mild	1
	Increased sputum	Lungs	Remote	Mild	1
	Increased sputum	Lungs	Possible	Moderate	1
	Migraine	HEENT	Remote	Severe	1
Pari LC	Bronchospasm	Lungs	Probable	Mild	1
	Chest Pain	Lungs	Remote	Moderate	1
	Hemoptysis	Lungs	Remote	Mild	1
	Increased Sputum	Lungs	Remote	Moderate	1
	Neck Stiffness	Misc.	Remote	Mild	1
	Posttussive Emesis	Misc.	Remote	Moderate	1

Adverse events were reported as follows:

Summary of Adverse Events(AE)

	Ultraneb	Sidestream	Pari LC	Total
No. of AE	29	18	15	62
No. of drug-related AE	11	7	6	24
No. of serious AE	1	1	1	3
Patients with AE	17	10	11	29
Patients with drug related AE	5	5	4	12
Patients with serious AE	1	1	1	3

One subject in each treatment arm experienced bronchospasm with the administration of aerosolized tobramycin. None of these episodes of bronchospasm were considered serious. The serious AEs reported were due to hospitalization in each case. Two patients were hospitalized for hemoptysis occurring two and six days after treatment with the Ultraneb and Sidestream nebulizers. These episodes of hemoptysis were considered unrelated to drug treatment. The Pari LC patient was hospitalized for chest pain one day after aerosol treatment. These adverse events resolved in all cases. Chest pain was considered remotely related to aerosol treatment.

The maximum serum concentrations measured using each of the nebulizers is shown in the table below. Overall, the peak serum concentration of tobramycin remained well below the trough levels used to monitor systemic tobramycin therapy. Again the reader is referred to the safety review by Marianne Mann, M.D. for a more detailed safety assessment of the individual clinical trials.

Maximum Serum Tobramycin Concentrations (µg/mL)

	Ultraneb	Sidestream	Pari LC
N	63	62	64
Mean (µg/mL)	0.81	0.76	0.58
S.D.	0.80	0.42	0.37
Median (µg/mL)	0.60	0.65	0.50

PC-TNDS-002 AND PC-TNDS-003
"A Phase III Placebo Controlled Clinical Trial to Study the Safety and Efficacy of Tobramycin for Inhalation in Patients with Cystic Fibrosis (CF)"
(M.O. Comment: The two phase III clinical trials in this NDA used identical protocols, and were designed with the plan to pool the results of the two studies. For the purposes of this review, the two phase III clinical trials will be discussed together. Where appropriate, information from the individual trials will be identified as 'from protocol 002' or 'from 003'. Otherwise it should be assumed that information applies to both of these studies. The objectives and study description given below is taken directly from an electronic version of the study protocol provided by the sponsor. It has been edited to apply to both protocols. Comments are inserted to highlight certain aspects of the protocols, and information which applies to only one protocol is identified. The protocol was also reviewed as part of an IND submission.)

Objectives: The overall objectives of this project are to establish the safety and efficacy of twice-daily administration of 300 mg of aerosolized tobramycin for 28 days, and the safety and efficacy of repeated, intermittent, short-term (28 days) therapy for 168 days in patients with CF who are chronically colonized with *P. aeruginosa* and who are clinically stable.

Primary Objectives

a) To determine if the change in FEV_1 from baseline is different in the aerosolized tobramycin-treated group, following each 28-day cycle of therapy, when compared with the placebo-treated group.

b) To determine if the change in *P. aeruginosa* density in the sputum from baseline is different in the aerosolized tobramycin-treated group, following each 28-day cycle of therapy, when compared with the placebo-treated group.

(M.O. Comment: Changes from baseline in FEV1 and sputum bacterial density were chosen as the primary efficacy endpoints by the sponsor. The choice of FEV1 as a primary endpoint is related to several studies of aerosolized tobramycin in the literature. These literature studies serve as the basis for the current off-label use of IV tobramycin in nebulizers. These objectives specify looking at results 'following each 28-day cycle'. However, they do not specify using visit 10 as the primary endpoint. The statistical methods section does discuss using repeated measures analytic methods for parameters measured at multiple timepoints during the trial.)

Secondary Objectives

a) To determine if the safety profile of patients receiving tobramycin for inhalation over a 168-day period is different from the placebo group.

b) To determine if anti-pseudomonas IV antibiotic use is reduced with three repeated short-term aerosolized tobramycin courses over a 168-day period compared to the placebo group.

c) To determine if the change from baseline FVC of the aerosolized tobramycin-treated group, following each 28-day cycle of therapy, is different from the placebo group.

d) To determine if the incidence of highly tobramycin-resistant (MIC $\geq$ 128 µg/mL) *P. aeruginosa* strains in the tobramycin-treated group is different following three 28-day courses of intermittent tobramycin for inhalation over a 168-day period compared to the placebo group.

e) To determine differences between the tobramycin-treated and placebo groups in morbidity measures including: incidence of hospitalization, hospital days, missed work/school days, and quality of well-being.

(M.O. Comment: Multiple secondary efficacy endpoints are included in this trial. While effects on FEV1 are important, the medical officer will also look to these secondary endpoints for evidence of clinical benefit from aerosolized tobramycin use. Secondary objectives regarding drug product safety and the development of resistance are the subject of another review.)

Patient Population: All patients with the underlying disease of CF, meeting the inclusion/exclusion criteria specified in this protocol, will be eligible for enrollment into the study. Investigators at the participating CF centers will select subjects from patients who meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

1. Able to give informed consent.
2. $\geq$ 6 years of age.
3. Documented sweat chloride $\geq$60 mEq/L by quantitative pilocarpine iontophoresis test (QPIT) or homozygosity for ΔF508 genetic mutation (or heterozygosity for two well characterized mutations) and two clinical findings consistent with CF.
4. $FEV_1 \leq 75\%$ and $\geq 25\%$ of predicted, based on gender, age and height.
5. *P. aeruginosa* present in a sputum/throat culture within 6 months prior to screening and a minimum of one screening visit.
6. Ability to perform pulmonary function tests.
7. Room air oximetry $\geq$ 88% saturation.

Exclusion Criteria

1. Administration of any anti-pseudomonas antibiotics by any route within 14 days prior to initial study drug administration.
2. Administration of any investigational drug within 4 weeks of study drug administration.
3. Positive serum pregnancy test. Test must be performed at screening and repeated prior to each period of drug administration. (Sexually active females must agree to use contraception during the study period.)
4. Hemoptysis ≥60 cc at any time within thirty days prior to study drug administration.
5. Known local or systemic hypersensitivity to aminoglycosides.
6. Serum creatinine ≥ 2 mg/dl, BUN ≥ 40 mg/dl, or an abnormal urine analysis defined as ≥ 2+ proteinuria.
7. G6PD deficiency.
8. History of sputum culture or throat swab culture yielding *B. cepacia* in the previous two years and/or sputum or throat swab culture yielding *B. cepacia* at screening. (Visit 1 or 2)
9. Abnormal chest X-ray, as described in Study Guidelines.

(M.O. Comment: Several points should be made here. An acceptable definition of cystic fibrosis is used. The age criterion is given due to the inability of young children to accurately perform PFT's. Inclusion criterion 6 also excludes older individuals who are unable to perform PFT's accurately. There is a requirement that subjects have evidence of chronic colonization of the airway with *P. aeruginosa*. The presence of this organism in sputum at two separate time points is adequate for this purpose. FEV_1 %predicted must be between 25% and 75%. Little more than half of children in the 6-12 year age group with CF would meet this requirement, while the majority of adolescents and adults are in this group. Patients who had *B. cepacia* on sputum culture during the two years prior to study were excluded. Sputum culture with *B. cepacia* in CF patients usually indicates colonization of the lungs with this organism. The hypothesis is that *B. cepacia* might become the predominant organism in a CF patient treated with TOBI. Since colonization with this organism is associated with a worse prognosis, this restriction is a reasonable safety precaution. Other criteria are reasonable restrictions for the safe use of tobramycin or for exclusion of patients experiencing an acute exacerbation.)

Study Flowchart: The chart on the following page is taken directly from the sponsor's protocol for easy reference in the discussion of the study design which follows.

Outline of Study Schedule

VISIT	1	2	3	4	5	6	7	8	9	10	11
Tx	Scr	Scr	Start	On	Stop	Off	Start	Stop	Start	Stop	FU
Week	-4	-2	0	2	4	6	8	12	16	20	24
Day	-28±2	-14±2	0±2	14±2	28±2	42±2	56±4	84±4	112±4	140±4	168±4
Patient Consent	X										
Patient History	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		[X] [1]				X			X	[X] [1]
Chest X-ray	X									X	
Clinical Evaluation	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Exacerbation Questionnaire	X						X			X	
Clinical Evaluation & Pulmonary Questionnaire	X	X	X	X	X	X	X	X	X	X	X
Sputum Specimen											
Microbiology[2]	X	X	X	X	X	X	X	X	X	X	X
• Tobramycin Level[3]			X							X	
Safety Labs	X	[X] [4]	X		X		X	X	X	X	[X] [4]
G6PD	X										
Serum Pregnancy Test	X		X				X		X		
Serum Tobramycin Conc.											
Pre[5]			X							X	
1hr Post[6]			X							X	
1-12hr Post[7]					X		X	X	X		
Spirometry											
Routine	X	X		X	X	X	X	X	X		X
Pre-dose			X[8]							X[8]	
30 minutes post			X[8]							X[8]	
Audiology[9]	X		X		X		X	X	X	X	
Study Drug											
Administered			X[10]							X[10]	
Dispensed			X[11]	X			X	X	X		
Accountability					X					X	
Randomization Form[12]	X	X									

Legend for Flow Chart:

[1] [X]=if findings at previous visit are abnormal, repeat procedures at baseline or at follow up (FU) visit

[2] Obtain pre-treatment; if patient is unable to produce a sputum specimen, a throat swab must be obtained

[3] Obtain 10 minutes after completion of aerosol administration

[4] Safety labs (hematology, serum chemistries and urinalysis) will be repeated if abnormal at previous visits

[5] Pre-dose specimen must be collected prior to administration of study drug

[6] Obtain 60 minutes after completion of aerosol administration (obtain from a peripheral site, not existing central or peripheral venous access)

[7] A minimum of 1 hour and a maximum of 12 hours must have elapsed since the last aerosol administration when obtaining serum for the drug concentration assay (obtain from a peripheral site, not existing central or peripheral venous access)

[8] At visits 3 and 10, spirometry must be performed prior to and 30 minutes following completion of the aerosol treatment to assess acute airway bronchospasm due to study drug

[9] Audiology will only be conducted at selected study sites

[10] The first dose of the study drug (Visit 3, treatment cycle 1) and the last dose of the study drug (Visit 10, treatment cycle 3) will be administered at the study site in the presence of the research coordinator

[11] Patient log diary, nebulizer(s), nose clips and Pulmo-Aide© compressor must also be dispensed at Visit 3

[12] Form must be faxed to PathoGenesis Corporation at Visits 1 and 2

Study Design: Two hundred moderately to severely ill patients with cystic fibrosis (CF) from up to 40 separate CF centers will be enrolled. **(M.O. Comment: Both studies exceeded enrollment of two hundred patients. Protocol 002 included 29 centers, and protocol 003 included 40 centers. All centers were located in the U.S.)** Each patient will undergo two screening evaluations to assess eligibility and obtain baseline microbiology and pulmonary function data. Following completion of screening, eligible patients will be randomized to receive either aerosol tobramycin or placebo (saline taste-masked with quinine) twice daily for 28 days, followed by a 28-day period with no treatment. This cycle will be repeated twice, for a total of three cycles. Scheduled study visits will be every two weeks for the first eight weeks of the treatment, and every four weeks thereafter. A follow-up visit will be performed four weeks after cessation of study therapy.

Informed consent will be obtained at the initial visit (Visit 1, week -4). Patient evaluations will occur every two weeks for the first 12 weeks of the study and every four weeks thereafter (refer to flow chart). At the screening visits (Visit 1, week -4 and Visit 2, week -2) each patient's medical history (including anti-pseudomonas antibiotic use) will be recorded and patient's current health status, pulmonary function, and sputum microbiology will be evaluated. Eligible patients will be randomized at the third visit (Visit 3, week 0) and treatment with study drug will be initiated. At each subsequent study visit, clinical evaluations (including pulmonary function) will be performed, interim histories will be reviewed, use of anti-pseudomonas antibiotics will be documented and sputum or throat swabs will be obtained for bacterial culture and antibiotic susceptibility testing. Blood and urine samples will be collected every four weeks throughout the study to assess multiple safety parameters. Pregnancy tests will be performed on female participants (if indicated) at baseline and prior to initiation of each study cycle. At selected centers, audiometry will also be performed every four weeks.

Screening Visit 1 (Day -28 ± 2)

1. Written informed consent
2. Medical history review (including concurrent illnesses, CF associated symptoms, current medications and dosages)
3. Physical examination by physician
4. Chest X-ray
5. Clinical evaluation including height, weight and vital signs and pulmonary exacerbation questionnaire
6. Sputum sample for bacterial culture. If patient is unable to produce sputum, a throat culture must be obtained.
7. Urine for dipstick analysis for proteinuria
8. Blood for hematology, serum chemistries and G6PD deficiency
9. Blood for serum pregnancy test (if applicable)
10. Spirometry
    a) Forced Expiratory Volume at one second (FEV_1)
    b) Forced Vital Capacity (FVC)
    c) Forced Expiratory Flow (FEF_{25-75})
11. Audiogram (at selected study sites)
12. Randomization form

Screening Visit 2 (Day -14 ± 2 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Clinical evaluation including weight and vital signs
3. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
4. Urine for dipstick analysis for proteinuria (only if abnormal at Visit 1)
5. Blood for hematology and serum chemistries (only if abnormal at Visit 1)
6. Spirometry
    a) Forced Expiratory Volume at one second (FEV_1)
    b) Forced Vital Capacity (FVC)
    c) Forced Expiratory Flow (FEF_{25-75})
7. Randomization form
8. Audiogram, if not done at Screening visit #1 (at selected study sites)

Baseline Visit 3 (day 0 ± 2 days)

Pre-treatment At the baseline visit, each patient will be evaluated to ensure that all selection criteria are satisfied and the following procedures will be completed:

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Physical examination by physician (only if abnormal at Visit 1)
3. Clinical evaluation including weight and vital signs
4. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
5. Urine for dipstick analysis for proteinuria
6. Blood for hematology and serum chemistries
7. Blood for serum tobramycin concentration (Blood must be obtained from a peripheral site, not existing central or peripheral venous access.)
8. Blood for pregnancy test (if applicable)
9. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
10. Audiogram (at selected study sites)

Treatment

1. Administer dose of aerosol study drug according to protocol

Post-Treatment

1. Obtain 10 minute post administration sputum sample for tobramycin concentration (if patient is able to expectorate sputum)
2. Obtain 30 minute post administration spirometry
3. Obtain 60 minute post administration serum for tobramycin concentration (Blood must be obtained from a peripheral site, not existing central or peripheral venous access.)
4. Dispense required study drug medication, nose clips, 2 Pari LC Jet+ nebulizers, Pulmo-Aide® compressor, and patient log diary

The research coordinator will train patient and/or family on administration of drug, maintaining and cleaning equipment, and how to complete the patient log diary.

Visit 4 (Day 14 ± 2 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes
2. Clinical evaluation including weight and vital signs
3. Sputum sample for bacterial culture. If he is unable to expectorate sputum, a throat culture must be obtained.
4. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
5. Review patient log diary

Visit 5 (Day 28 ± 2 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Clinical evaluation including weight and vital signs
3. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
4. Urine for dipstick analysis for proteinuria
5. Blood for hematology and serum chemistries
6. Blood for serum tobramycin concentration collected a minimum of 1 hour and a maximum of 12 hours post-treatment (Blood must be obtained from a peripheral site, not existing central or peripheral access.)
7. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
8. Audiogram (at selected participating study sites)
9. Drug accountability and compliance assessment determined by reviewing patient log diary

Visit 6 (Day 42 ± 2 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Clinical evaluation including weight and vital signs
3. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
4. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})

Visit 7 (Day 56 ± 4 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Physical examination by physician
3. Clinical evaluation including height, weight and vital signs and pulmonary exacerbation questionnaire
4. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
5. Urine for dipstick analysis for proteinuria
6. Blood for hematology and serum chemistries
7. Blood for serum tobramycin concentration collected a minimum of 1 hour and a maximum of 12 hours post-treatment (Blood must be obtained from a peripheral site, not existing central or peripheral venous access.)
8. Blood for pregnancy test (if applicable)
9. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
10. Audiogram (at selected study sites)
11. Dispense required study drug medication and patient log diary

Visit 8 (Day 84 ± 4 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Clinical evaluation including weight and vital signs
3. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
4. Urine for dipstick analysis for proteinuria
5. Blood for hematology and serum chemistries
6. Blood for serum tobramycin level collected a minimum of 1 hour and a maximum of 12 hours post-treatment (Blood must be obtained from a peripheral site, not existing central or peripheral venous access.)
7. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
8. Audiogram (at selected study sites)
9. Drug accountability and compliance assessment determined by reviewing patient log diary

Visit 9 (Day 112 ± 4 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Clinical evaluation including weight and vital signs
3. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
4. Urine for dipstick analysis for proteinuria
5. Blood for hematology and serum chemistries
6. Blood for serum tobramycin level collected a minimum of 1 hour and a maximum of 12 hours post-treatment (Blood must be obtained from a peripheral site, not existing central or peripheral venous access.)
7. Blood for pregnancy test (if applicable)
8. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
9. Audiogram (at selected study sites)
10. Dispense required study drug medication and patient log diary

Visit 10 (Day 140 ± 4 days)

<u>Pre-treatment</u>

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Physical examination by physician
3. Clinical evaluation including height, weight and vital signs and pulmonary exacerbation questionnaire
4. Chest X-ray
5. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
6. Urine for dipstick analysis for proteinuria
7. Blood for hematology and serum chemistries
8. Blood for serum tobramycin level (Blood must be obtained from a peripheral site, not existing central or peripheral venous access.)
9. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})

Treatment

1. Administer dose of aerosol study drug according to protocol

Post-treatment

1. Obtain 10 minute post administration sputum sample for tobramycin concentration (if patient is able to expectorate sputum)
2. Obtain 30 minute post administration spirometry
3. Obtain 60 minute post administration serum for tobramycin concentration (Blood must be obtained from a peripheral site, not existing venous central or peripheral venous access.)
4. Audiogram (at selected study sites)
5. Drug accountability and compliance assessment determined by final review of patient log diary

Follow-up Visit 11, (Day 168 ± 4 days)

1. Interim history (including adverse events, changes in CF symptoms, and medication changes)
2. Physical examination by physician (only if abnormal at Visit 10)
3. Clinical evaluation including weight and vital signs
4. Sputum sample for bacterial culture. If patient is unable to expectorate sputum, a throat culture must be obtained.
5. Urine for proteinuria (only if abnormal at Visit 10)
6. Blood for hematology and serum chemistries (only if abnormal at Visit 10)
7. Spirometry
   a) Forced Expiratory Volume at one second (FEV_1)
   b) Forced Vital Capacity (FVC)
   c) Forced Expiratory Flow (FEF_{25-75})
8. Complete final patient assessment (Case Report Form)

(M.O. Comment: There are no significant issues in the outline of study procedures. Case report forms follow a similar pattern, and the study appears to have been conducted as planned in the protocol.)

Evaluability Criteria: From the protocol, two populations were defined for efficacy analysis:

a) Intent To Treat
Those patients who received treatment and who have at least one measurement on any clinical efficacy parameter at 4 weeks will be included in the intent to treat analysis.

b) Efficacy Evaluable
Those patients who complete the three treatment cycles of the study with no protocol violations will be included in the efficacy evaluable analysis. In the event of a protocol violation, the evaluability of the patient will be determined by the medical monitor without knowledge of the treatment assignment. In addition, compliance will be considered.
(M.O. Comment: Although the ITT definition includes a statement which requires some clinical efficacy parameter at 4 weeks, the ITT group used in the analysis included all patients who received at least one dose of study drug. This change of ITT population was made after discussion with the FDA The medical officer analysis will focus on the ITT population. The following section on efficacy measures is from the sponsor's integrated summary of efficacy.)

Measures of Efficacy:
To support an indication of improvement and maintenance of pulmonary function, reduction in *P. aeruginosa* sputum bacterial density, reduction in hospitalization and reduction in the use of anti-pseudomonal antibiotics in cystic fibrosis patients infected with *P. aeruginosa*, the following measurements were assessed in the two trials:

> The difference between the TOBI and placebo groups in the mean relative change from baseline to Visit 10 in FEV_1 % predicted
>
> The difference between the TOBI and placebo groups in the mean change from baseline to Visit 10 in $\log_{10}$ CFU/g of sputum

(M.O. Comment: The above two measures were the primary efficacy endpoints chosen by the sponsor after discussion of the original protocol with the division. The original protocol had planned to use the change from baseline to the

28 day visit. However, the sponsor was informed that in order to garner an indication for more than a one month treatment course, they would need to use a measurement closer to the end of the trial. Prior studies in the literature supported the efficacy of inhaled tobramycin over a 28 day period, but the sponsor still had concerns about the possibility of decreased efficacy over long term use. This is the most likely reason for the use of a repeated measures analysis. This allows separate analysis of the results of a single 28 day cycle of inhaled tobramycin use.

Both of these parameters will still be used as the primary efficacy endpoint for the analyses, but some concerns should be noted. The validity of quantitative sputum cultures are in question. It is well recognized that some patients with CF are chronically colonized with *Pseudomonas aeruginosa*. When these subjects are treated with systemic antibiotics, the organisms may be suppressed, but the majority of patients continue to harbor *P aeruginosa* isolates. Thus, the usual microbiologic categories (e.g. eradication, superinfection) can not be used. This quantitative measurement is an effort to demonstrate some antimicrobial effect, but questions remain as to interpretation of these values. While the Division of Pulmonary Drug Products does use change in FEV1 % predicted in the efficacy analysis of bronchodilators, these are acute changes. There is some question as to how well long-term changes in PFT's would correspond to actual clinical benefit. As a result, much of the medical officer analysis will focus on other measures of clinical benefit as given by the sponsor below.)

The risk of hospitalization for patients treated with TOBI relative to placebo

The number of days hospitalized compared between the TOBI and placebo groups

The risk of treatment with IV anti-pseudomonal antibiotics for patients treated with TOBI relative to placebo

The difference between the TOBI and placebo groups in the mean relative change from baseline to Visit 10 in FVC % predicted

Statistical Analysis:

Data Analysis Methods: Univariate comparisons between the study groups will be based on non-parametric Wilcoxon statistics for continuous variables and chi-squared statistics for categorical or ordinal variables. Comparisons will also be adjusted for relevant covariates using linear regression analysis methods (or ANOVA) for continuous variables and logistic regression analysis methods for dichotomous categorical variables. Continuous variables will be analyzed to determine if they need to be transformed prior to analysis to ensure approximately symmetric distributions. Repeated measures methods will be used for analyses involving parameters measured at several time points in the 168 day treatment period. For this, standard repeated measures or generalized estimating equation methods can be employed. This methodology can be used with both continuous and discrete data and is similar to standard repeated measures ANOVA except that the correlation structure in the data need not be specified in advance. All hypothesis tests and p-values will be two sided.

(M.O. Comment: Primary analyses of PFT's and sputum CFU's used the repeated measures ANOVA. However, the sponsor chose to focus on the change between visit 3 (baseline) and visit 10 (end of therapy visit for the third cycle) as the primary efficacy endpoint. The medical officer review will look at the results over the entire period of study. Since this treatment is being used as a chronic treatment, it seems more appropriate to investigate the changes in pulmonary function over the entire period of study. The sponsor had chosen to focus on data from visits 5 and 10 because these visits occur on the last day of drug administration for the first and third cycle of treatment. They were concerned that the effect on PFT's from the on drug period would wane during the off-drug period. The PFT results, particularly FEV_1 results, will be discussed in more detail in the results section of this document.)

Patient Characteristics and Baseline Data: The two study arms will be compared with regard to age, gender, baseline PFT values (median of visits 1, 2 and 3), center, therapy with rhDNase, sputum production and MICs to tobramycin. Only baseline data at visits 1, 2 and 3 will be included in these analyses.

Clinical Efficacy Data:

Pulmonary Function Tests (PFT)
The two study arms will be compared with regard to their average percent change from baseline to 4 weeks. Baseline FEV_1 and FVC values will be calculated using the median of pre-treatment values measured at visits 1, 2 and 3. The percent change from baseline will be calculated as:

(PFT at 4 weeks - baseline PFT)/(baseline PFT)

Similarly, percent change from baseline to 12 weeks and from baseline to 20 weeks will be calculated and compared between two study arms. In each case the baseline PFT values will be the median of those measured at visits 1, 2 and 3.

(M.O. Comment: After meeting with the division in a meeting, before the blind was broken on the data, it was agreed that the data from visit 3 would be used as the baseline value. It was noted by the sponsor that some investigators treated patients with IV antibiotics between visits 1 and 2. The sponsor was concerned that this would raise the baseline PFT measurement and lower the baseline sputum bacterial density. The sponsor provided data which demonstrated that the variability and mean was not significantly different for each individual visit compared to the median of the three. The use of visit 3 data as baseline was acceptable. Another issue regards the calculation of percent {relative} change from baseline. Since the PFT values at each timepoint are % predicted values, they are reported as a percentage of the expected value based on a subject's height and age. The relative change in FEV_1 used as an outcome variable is presented as a percentage of the baseline value, which is itself a percentage of the expected value for age and height. The effect of looking at a relative change rather than an absolute change is to inflate the number produced. This calculation was chosen, in part, because this was the value used to represent changes in FEV_1 in the product label for Pulmozyme®. While this may be an appropriate way to represent the data in the product label, the M.O. will also look at calculations based on raw FEV_1 and absolute change. Statistical differences are not expected unless there is a large effect of change in age or height over the 6 month period of the study.)

PFT values over the whole 168 day study period will be plotted and modeled simultaneously using repeated measures analyses. This allows comparison of the study arms with regard to: (i) trends over the 168 day treatment period, (ii) average change from baseline over the 168-day treatment period, (iii) comparisons between early and later treatment effects and (iv) PFT parameters 4 weeks after cessation of therapy for each of the three treatment cycles.

Sputum Production and Bacterial Density
The proportion of patients producing sputum will be calculated by treatment arm at baseline and after each treatment cycle. Of patients who produce sputum at baseline (during at least one of visits 1, 2, and 3), the proportion still producing sputum will be calculated and compared between study arms after each treatment cycle.

For patients who produce sputum, bacterial densities will be analyzed on a logarithmic scale. Change from baseline (defined analogously as for PFT parameters) will be compared between the study arms at 4 weeks, at 12 weeks, and at 20 weeks. Treatment effects over the entire 168 day period will be plotted and modeled using repeated measures analyses.

Antibiotic Use
Total days of non-aerosol anti-pseudomonas antibiotic administration will be calculated for each patient during weeks 0-24. Calculations will be performed for IV and oral therapy separately as well as combined. In addition, the two study groups will be compared by survival analysis methods [16, 17]. The number and duration of non-aerosol anti-pseudomonas therapy episodes (IV and oral) will be calculated and compared.

Morbidity Endpoints
The total number of hospital days, infusion days and missed school/work days will be compared over the 168-day study period and changes in quality of well-being will be compared between the treatment groups.
(M.O. Comment: The reviewer will focus on the hospitalizations for lower respiratory infection. The sponsor was able to distinguish hospitalizations for lower respiratory infection from upper respiratory, GI, or other by diagnostic codes. Other causes represented less than five percent of all hospitalizations during the study period, and were equivalent in the placebo and TOBI groups.)

Study Results:

Demographics: The following table shows the numbers and percentages of subjects at various points in the study. Overall, the two arms in each study were comparable. Reasons for withdrawal were similar between the two groups, except for a slightly higher number of subjects with deteriorations in the placebo group. This is supportive evidence of some clinical benefit to use of TOBI, given that 5(19.2%) of withdrawals in the TOBI group vs. 14(46.7%) of withdrawals in the placebo group were for deterioration in pulmonary status. Premature withdrawal from study is discussed further in the safety review by Marianne Mann, M.D.

Patient Disposition

	PC-TNDS-002			PC-TNDS-003		
Number (%) of Patients	TOBI	Placebo	Total	TOBI	Placebo	Total
Screened			276			387
Screening Failure			53			90
Enrolled	109 (100.0)	114 (100.0)	223 (100.0)	149 (100.0)	148 (100.0)	297 (100.0)
Completed	96 (88.1)	100 (87.7)	196 (87.9)	136 (91.3)	132 (89.2)	268 (90.2)
Withdrawn	13 (11.9)	14 (12.3)	27 (12.1)	13 (8.7)	16 (10.8)	29 (9.8)
Cycle 1	4 (3.7)	8 (7.0)	12 (5.4)	5 (3.4)	7 (4.7)	12 (4.0)
Cycle 2	6 (5.5)	5 (4.4)	11 (4.9)	6 (4.0)	5 (3.4)	11 (3.7)
Cycle 3	3 (2.8)	1 (0.9)	4 (1.8)	2 (1.3)	4 (2.7)	6 (2.0)

Patients were similar with respect to stratification variables and demographics across treatment arms, and across both studies as seen in the table below.

Patient Demographic and Stratification Data at Screening(ITT)

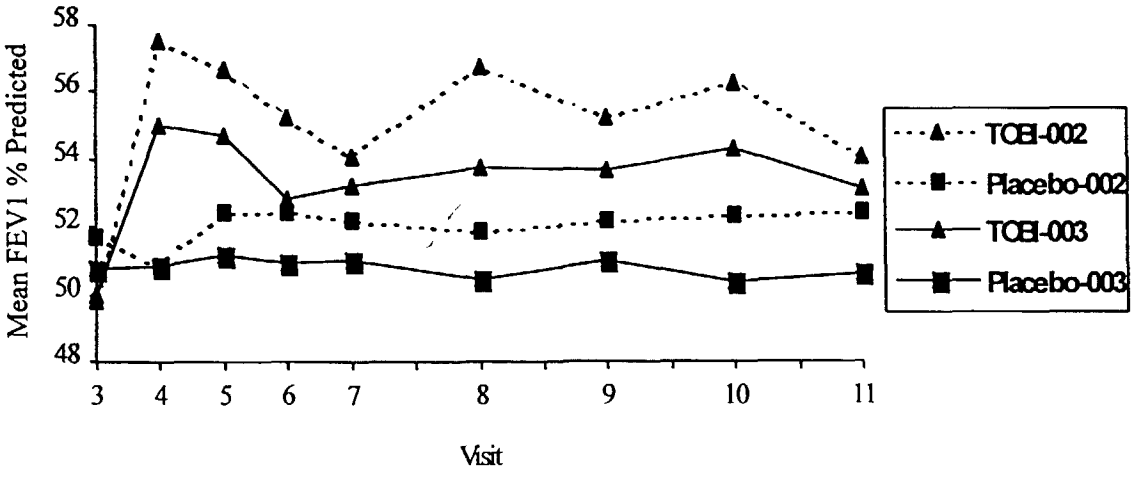
	PC-TNDS-002		PC-TNDS-003		Pooled(002/003)	
Number (%) of Patients	TOBI 109	Placebo 114	TOBI 149	Placebo 148	TOBI 258	Placebo 262
Gender:						
Male	63 (57.8)	59 (51.8)	86 (57.7)	73 (49.3)	149 (57.8)	132 (50.4)
Female	46 (42.2)	55 (48.2)	63 (42.3)	75 (50.7)	109 (42.2)	130 (49.6)
Mean Age in Years (STD)	20.5 (9.33)	19.8 (10.16)	21.0 (9.59)	21.2 (9.84)	20.8 (9.46)	20.6 (9.98)
Age Group:						
6 - < 13 years	26 (23.9)	30 (26.3)	29 (19.5)	31 (20.9)	55 (21.3)	61 (23.3)
13 - < 18 years	24 (22.0)	32 (28.1)	39 (26.2)	35 (23.6)	63 (24.4)	67 (25.6)
≥ 18 years	59 (54.1)	52 (45.6)	81 (54.4)	82 (55.4)	140 (54.3)	134 (51.1)
FEV_1 % Predicted:						
< 50%	50 (45.9)	56 (49.1)	72 (48.3)	72 (48.6)	122 (47.3)	128 (48.9)
≥ 50%	59 (54.1)	58 (50.9)	77 (51.7)	76 (51.4)	136 (52.7)	134 (51.1)
rhDNase Therapy						
No	24 (22.0)	28 (24.6)	36 (24.2)	30 (20.3)	60 (23.3)	58 (22.1)
Yes	85 (78.0)	86 (75.4)	113 (75.8)	118 (79.7)	198 (76.7)	204 (77.9)
Tobramycin baseline MIC (*P. aerug*)						
< 8 g/mL	95 (87.2)	98 (87.5)	123 (82.6)	125 (84.5)	218 (84.5)	223 (85.8)
≥ 8 g/mL	14 (12.8)	14 (12.5)	26 (17.4)	23 (15.5)	40 (15.5)	37 (14.2)

Primary Outcomes: PFT analysis--The following chart is a summary of the primary efficacy outcome as reported by the sponsor. The table shows the relative change from baseline (visit 3) to visit 10 in FEV_1 %predicted, FVC % predicted, and absolute change in Log_{10} CFU/g sputum. The limitations of these outcome variables include the fact that only two points in time are evaluated (visit 3 and visit 10) although values are available from multiple time points. Also, the PFT data are analyzed based on a percent change from baseline. The results do show a statistically significant difference in the relative change in FEV_1 %predicted, FVC %predicted, and sputum bacterial density in each of the two pivotal studies PC-TNDS-002 and PC-TNDS-003.

RELATIVE CHANGES IN PRIMARY ENDPOINTS

	Protocol 002			Protocol 003		
	Mean Change		P-value	Mean Change		P-value
Endpoint	TOBI	Placebo	for Diff	TOBI	Placebo	for Diff
FEV_1 %Pred	12.02	-.52	<.001	8.70	-2.72	<.001
FVC %Pred	8.72	-.89	.001	7.07	-1.55	<.001
log_{10}(CFU)	-.87	.30	<.001	-.62	.37	<.001

The following graph shows the mean FEV_1 %predicted for the TOBI and placebo groups in the two pivotal studies. The graph shows that a difference is present between TOBI and placebo in each of the two studies, and at each time point during the study. Similar results were seen when FVC was displayed graphically in each of the two clinical trials.



The following table is from the statistical review for TOBI by Thomas Hammerstrom Ph.D. The reader is referred to the statistical review for details of statistical methods. The table shows the mean changes in PFT's and bacterial sputum density from baseline over the entire study period. The values were calculated by linear interpolation of raw PFT's of individual subjects (in effect, determining an area under the curve for the difference from baseline PFT vs. time). Raw FEV_1 and FVC (in liters) is used in this interpolation. The FEV1 % and FVC% were calculated by dividing the mean change in FEV_1 and FVC by their respective baseline values. These mean relative changes are calculated because the raw FEV_1 and FVC vary directly with age. The FEV1 % and FVC% correct for this age effect, but do not inflate the mean relative change as calculated by the sponsor.

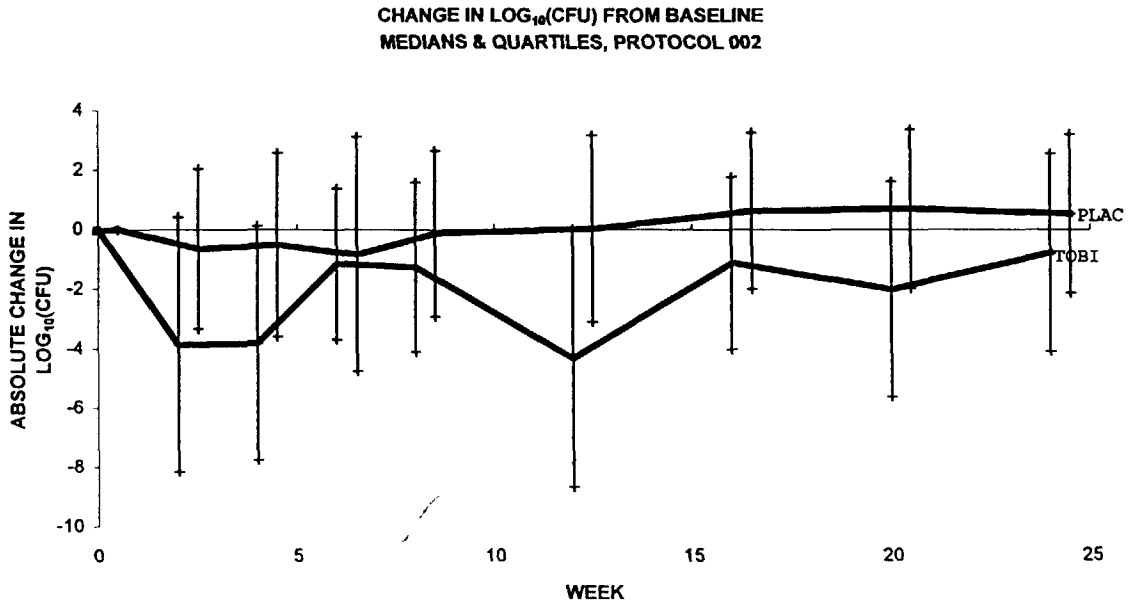
MEAN CHANGES OVER 24 WEEKS IN PFT'S, LOG_{10}(CFU'S) AND RANDOMIZATION-BASED P-VALUES FOR TREATMENT EFFECT

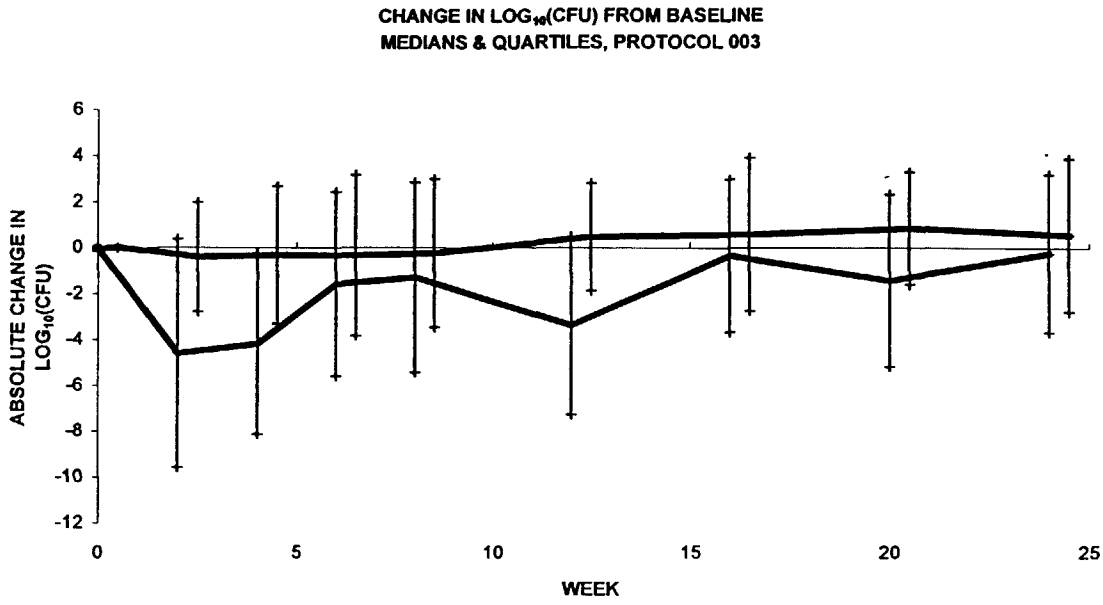
	Mean Change		P-value for
	TOBI	Placebo	Difference
Prot 002			
FEV_1	.126 liters	-.016	<.001
FVC	.114 liters	-.010	.0011
FEV1 %	11.18 %	.18 %	.002
FVC%	7.42 %	.71 %	.006
LOG_{10}(CFU)	-2.22 log count	.08	<.001
Prot 003			
FEV_1	.097 liters	-.028	<.001
FVC	.098 liters	-.008	.0013
FEV1 %	7.15 %	-.90 %	<.001
FVC%	5.38 %	.29 %	.0011
LOG_{10}(CFU)	-2.09 log count	.28	<.001

The data indicate that a statistically significant increase in the PFT values was seen in the TOBI group compared to placebo. This was true both for the raw values

as well as for the mean relative change. These results and the graph displayed on page 30 show that there is a statistically significant increase in FEV_1 that is present within two weeks after starting TOBI treatment and is sustained during the off drug periods. This brings into question the possibility that other treatment regimens may be as effective in improving PFT's, while decreasing drug exposure.(e.g.. two weeks of TOBI use every three months) The PFT analysis included subgroup analysis stratified by age group, gender, prior DNAse use, prior hospitalization, prior antibiotic use, baseline FEV_1 %predicted, and baseline MIC. No obvious interactions were identified.

Bacterial Sputum Density--The analysis of sputum bacterial density by the sponsor and the FDA reviewer are provided with the PFT results above. Sputum bacterial density is an experimental method of determining the number of colony forming units of *Pseudomonas aeruginosa* per gram of sputum. A graph of the sputum bacterial density vs. time is provided for each of the two protocols. Statistical analyses by both the sponsor and the FDA statistical reviewer indicate a statistically significant difference in sputum bacterial density between the TOBI and placebo groups in each protocol.





A clear pattern of decrease in bacterial sputum density during on drug periods with return toward baseline during off drug periods is seen. It is also noted that the effect of TOBI on sputum bacterial density appears to decrease with successive treatment cycles. The reason for this is unclear. One possible explanation was that fewer TOBI patients were producing sputum samples. However, the number of sputum samples did not differ greatly between the TOBI and placebo groups. It was of interest that both the TOBI and placebo groups had fewer sputum samples at on drug visit compared to off drug visits. This was especially true of the change from visit three to visit four, the start of the first cycle. A decrease in sputum samples may be the result of humidification from the aerosol alone, rather than the TOBI.

There also remains some question of the value of sputum bacterial density as a measure of pulmonary status in CF patients. This is an attempt to fit sputum colonization with *Pseudomonas aeruginosa* into the traditional model of bacterial eradication in antibiotic trials. Traditionally in antibiotic trials, the presence or absence of a pathogen in appropriate culture at baseline and outcome visits is used as an objective means of determining antibiotic effect. It is likely that bacterial sputum density is related more to the growth characteristics of the *Pseudomonas* or other organisms present, the residual antibacterial effect of the

sputum in individual patients, and the characteristics of the sputum that allow it to act as a growth medium. While the lower sputum bacterial density in TOBI patients during on drug periods is probably related to the presence of tobramycin in the sputum, there is no correlation between the sputum bacterial density and a subject's pulmonary status.

Secondary Outcomes: There are several secondary outcomes in these trials. The sponsor designed identical pivotal protocols (PC-TNDS-002 and PC-TNDS-003) to combine the data from both trials for the analysis of the secondary outcomes. Secondary outcomes include hospitalizations, antipseudomonal antibiotic use, and missed work/school days. These outcomes are discussed individually in the following sections. For hospitalizations and antibiotic use, the sponsor did not specify beforehand the analyses to be performed. Generally, the results within a particular protocol were consistent with regard to these secondary outcomes. However, the two protocols differed in being able to show statistical significance for some of these results.

Hospitalizations--The following chart is a summary of the sponsor's data on hospitalization. These data include all hopspitalizations for any reason. The sponsor chose to report the results as a relative risk of hospitalization based on the percentage of patients hospitalized at the end of the study.

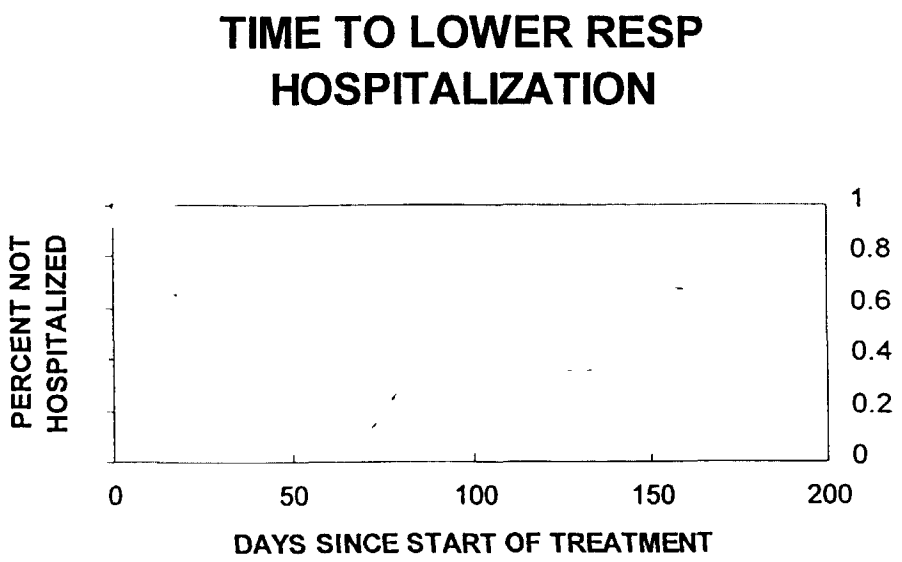
RELATIVE RISKS & DURATIONS OF HOSPITALIZATION
FOR LOWER RESP. ILLNESS, TOBI/PLACEBO

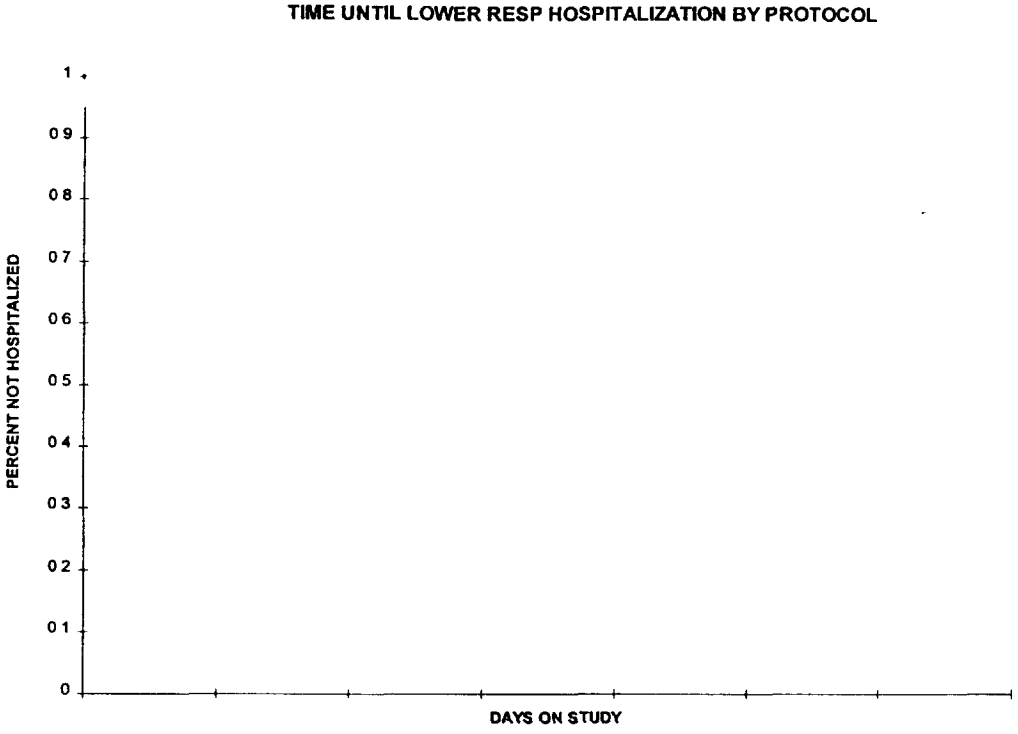
	Protocol 002		Protocol 003		Pooled	
	TOBI	Placebo	TOBI	Placebo	TOBI	Placebo
% Hospitalized	28%	45%	43%	45%	37%	45%
Relative Risk	.557		.891		.744	
95% Con. Limits	.356-.871		.631-1.258		.567-.975	
Mean Days in Hosp	4.6	9.1	5.5	7.4	5.1	8.1
P-value for Days	.008		.57		.03	

The sponsor recorded all hospitalizations that occurred in subjects during the study period. These hospitalizations were classified under four general categories. The main

category of interest is lower respiratory tract infections. Other categories include Upper respiratory tract infection (usually sinusitis), GI disease (usually related to pancreatic insufficiency), and 'others'. Hospitalizations for the latter three categories were even between the two treatment arms in each study and represented no more than 5% of all hospitalizations. For the remainder of this section the term hospitalization refers to hospitalization for a lower respiratory tract infection.

The medical officer and FDA statistician chose to investigate time to hospitalization for lower respiratory tract infection using Kaplan-Meier curves. The following graphs present time to hospitalization for the combined data followed by data for the individual protocols. The table that follows displays the p-values obtained by the Wilcoxon and Log-Rank Tests for the Kaplan-Meier curves. The Wilcoxon test was considered by the medical officer to be the more appropriate statistical method, since the log rank test places more emphasis on the early part of the Kaplan-Meier curve. However, agreement between the two tests is preferable. Patients who were early withdrawals due to lack of effect generally had already received IV treatment or had been hospitalized prior to withdrawal from study. Most of the censored subjects left the study due to reasons such as moving to another city. The medical officer considers censoring these subjects appropriate, but the p-values for early withdrawals as treatment failures are also given.





P-VALUES FOR TESTS OF TREATMENT EFFECT
ON TIMES TO HOSPITALIZATION

	WILCOXON TEST			LOG-RANK TEST		
PROTOCOL	002	003	BOTH	002	003	BOTH
DROP-OUTS CENSORED	.029	.60	.11	.13	.44	.16
DROP-OUTS AS FAILURES	.02	.49	.06	.11	.38	.12

For the time to hospitalization data, the p-value is different for the wilcoxon test vs. the log rank test in protocol 002. This may be a result of the early focus of the log rank test. The difference between the TOBI and placebo arms continues to widen as time passes. In looking at the results above and those reported by the sponsor, there is a consistent difference seen between the two protocols. The time to hospitalization and mean number of hospital days show a statistically significant treatment difference in protocol 002. However, the null hypothesis of no treatment difference can not be rejected for protocol 003. Since protocol 003 was the larger trial, this is not due to lack of statistical power for protocol 003. Neither

the sponsor nor the medical officer were able to determine the reason for the difference between the two protocols. Both trials used the same protocol. Both studies were multicentered, using 29 CF centers in protocol 002 and 40 CF centers in protocol 003. These centers were all in the United States, and no differences in geographic distribution were noted. The baseline demographics were similar for subjects in both protocols. Both protocols were run concurrently. No obvious differences in hospitalization date was seen during the trial. This might have played a role if an epidemic of influenza or other viral illness occurred during one trial but not another, but this was not the case. All centers were sufficiently small such that any single center should not have been able to contribute to the difference in the two protocols.

Kaplan-Meier curves of time to hospitalization were used for subset analysis. These were not planned analyses, and the study was not powered sufficiently to demonstrate a difference in these subgroups. Subsets were stratified by age group, gender, prior DNAse use, prior hospitalization, prior antibiotic use, baseline FEV_1 %predicted, and baseline MIC. No statistically significant treatment effects were seen although there was a trend toward a larger treatment effect in the younger age group(6-12 years), subjects with baseline FEV_1 % predicted greater than 50%, and females.

What remains is that the sponsor was unable to demonstrate that the incidence of hospitalization for lower respiratory tract infection was decreased over the six month period of study in TOBI patients compared to placebo. The individual trials yielded contradictory results and the combined data did not achieve statistical significance. The sponsor was able to show a decrease in the mean duration of hospitalization in TOBI patients compared to placebo. Part of this is related to the fact that fewer subjects in the TOBI arm were hospitalized. A difference is seen when comparing results from the two protocols. However, the planned secondary analysis using the combined data did show a decrease in mean days of hospitalization.

Anti-pseudomonal Antibiotic Use-Similar analysis methods to those used for hospitalizations were applied to antibiotic use. Both the sponsor and the medical reviewer used the same definition for antibiotic use. Unless otherwise noted, antibiotic use refers to the use of parenteral and/or oral antibiotics which have activity against *Pseudomonas aeruginosa*. The chart on the following page summarizes the sponsor's results on antibiotic use. Similarly to

hospitalization, the sponsor chose to report a relative risk of antibiotic use based on the percentages at the end of the study.

RELATIVE RISKS & DURATIONS OF ANTI-PSEUDOMONAL ANTIBIOTIC USE, TOBI/PLACEBO

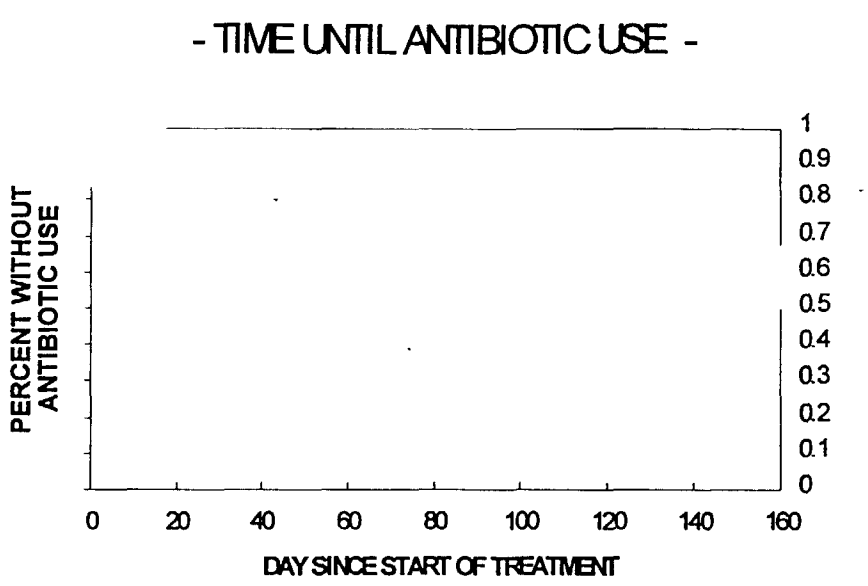
	Protocol 002		Protocol 003		Pooled	
	TOBI	Placebo	TOBI	Placebo	TOBI	Placebo
% IV Antibiotic Use*	33%	54%	43%	50%	39%	52%
Relative Risk	.512		.746		.640	
95% Con. Limits	.339-.773		.533-1.045		.494-.830	
Mean Days of IV Use*	8.8	14.6	10.1	13.7	9.6	14.1
P-value for Days	.002		.112		.001	
Mean Days of IV or Oral Use	20.1	29.5	28.0	33.6	24.7	31.8
P value for Days	.001		.08		<.001	

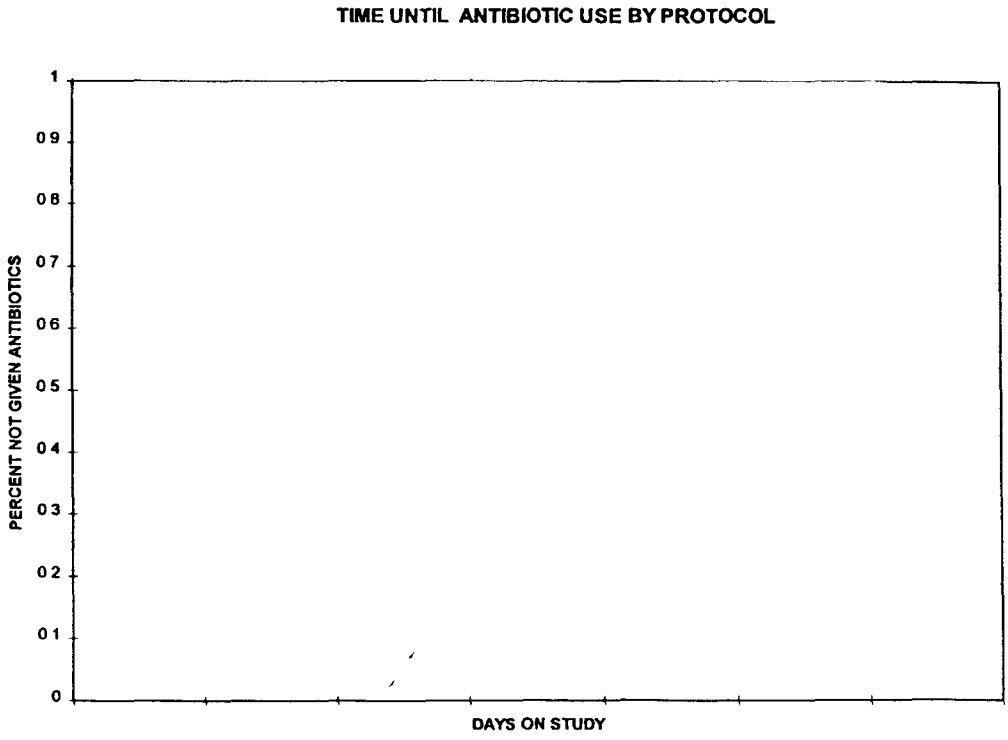
*Includes use of parenteral anti-pseudomonal agents only

Kaplan-Meier curves were used to investigate time to antibiotic use in the study population. The graphs on the following page present the time to antibiotic use for the pooled data, and for the individual protocols. The table below shows the p-values obtained from the Wilcoxon and Log-Rank Tests for the Kaplan-Meier curves. The same arguments for preference for the Wilcoxon test and censoring dropouts are equally valid for antibiotic use as for hospitalization.

P-VALUES FOR TESTS OF TREATMENT EFFECT ON TIMES TO ANTIBIOTIC USE

	WILCOXON TEST			LOG-RANK TEST		
PROTOCOL	002	003	BOTH	002	003	BOTH
DROP-OUTS CENSORED	.0015	.18	.004	.016	.22	.019
DROP-OUTS AS FAILURES	.001	.11	.003	.016	.17	.016


- TIME UNTIL ANTIBIOTIC USE -
PERCENT WITHOUT ANTIBIOTIC USE
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
140
160
DAY SINCE START OF TREATMENT


TIME UNTIL ANTIBIOTIC USE BY PROTOCOL
PERCENT NOT GIVEN ANTIBIOTICS
1
09
08
07
06
05
04
03
02
01
0
DAYS ON STUDY

The time to antibiotic use data are similar to the hospitalization data in that there is a difference between the two protocols. Again, the reason for this difference between the trials is unknown. In protocol 003 there seems to be a greater tendency toward a treatment effect on antibiotic use than there was for hospitalization. As a result, the pooled data show a statistically significant difference between the TOBI and placebo group in the time to antibiotic use. This is independent of the statistical test chosen. The sponsor data on mean days of IV antibiotic use or combined IV/oral antibiotic use showed similar results. Subset analyses for time to antibiotic use were performed. Stratification variables included age group, gender, prior DNAse use, prior hospitalization, prior antibiotic use, baseline FEV_1 %predicted, and baseline MIC. There were no statistically significant results seen. There was again a tendency toward greater treatment in the youngest age group and in females.

Missed School/Work Days-Subjects were asked to report the number of days of school or work that were missed since the last visit at each study visit. the results were than tabulated by cycle and overall by the sponsor. These results are shown below. A wilcoxon rank-sum test was used to compare treatment groups. The p-values are reported. These data follow the same trend seen in the other secondary outcomes in that a difference is seen in protocol 002 but not in protocol 003.

Mean Days of School/Work Missed

	Protocol 002			Protocol 003		
	TOBI	Placebo	p-value	TOBI	Placebo	p-value
Cycle 1	1.6	3.3	0.018	1.3	2.0	0.033
Cycle 2	1.7	2.7	0.087	1.9	2.0	0.596
Cycle 3	1.7	2.8	0.490	2.1	1.9	0.913
Overall	5.0	8.4	0.062	5.2	5.8	0.226

The sponsor also provided some data on investigator assessment and the patient or parents' treatment assessment during the trial. Patients were assessed as better, worse, or unchanged. Data are not presented for the patient or parent assessments because of concerns with missing data. There was a statistically significant treatment effect

reported for overall assessment in both protocols. The responses for TOBI vs. placebo at the end of study were 33% vs 18% better and 14% vs 23% worse in protocol 002 (p-value =.005), and with 34% vs 17% better and 13% vs 24% worse in protocol 003 (p-value <.001).

Treatment Effect and baseline MIC: The issues of development of tobramycin resistance during the clinical trials were discussed in detail in the safety review by Marianne Mann, M.D. The reader is referred to that document for information on the development of resistance. This section is a brief discussion of the modeling of baseline MIC and treatment response. In the sponsor analysis, an MIC breakpoint of 8 µg/mL was used as a baseline characteristic to differentiate subjects with "sensitive" vs. "resistant" organisms. This is based on the MIC breakpoint for intravenous tobramycin. In an attempt to estimate any lack of treatment response caused by resistance to tobramycin, the statistical reviewer developed polynomial regressions of the difference between TOBI and placebo for several outcome variables vs baseline MIC. The reader is referred to the statistical review by Thomas Hammerstrom, Ph.D. for the statistical issues surrounding these models. It is important to note that they are based on some unverified assumptions, and the information provided for MIC=32 µg/mL or greater is limited. This can be seen in the graphs as a widening of the confidence interval as the MIC increases.

The following two pages show graphs of the polynomial regression models. They are directly from the statistical review. Although there are not enough patients with high baseline MIC to have confidence in the effectiveness of the drug, there also is not any indication of decreasing effect at higher MIC. The only possible exception to this statement is in the polynomial for sputum bacterial density. In this curve, a positive slope starts to increase between MIC values of 8 to 128 µg/mL. The curve for risk of hospitalization also shows a similar tendency toward 1 at middle values of MIC. However, there is no obvious breakpoint for any of these curves. The curve for changes in FEV_1 does not indicate any loss of effect for TOBI at higher MIC values. Overall these polynomial regression models do not provide support for the choice of a MIC breakpoint, but the level of confidence we have in the effectiveness of TOBI at high MIC's is not strong.

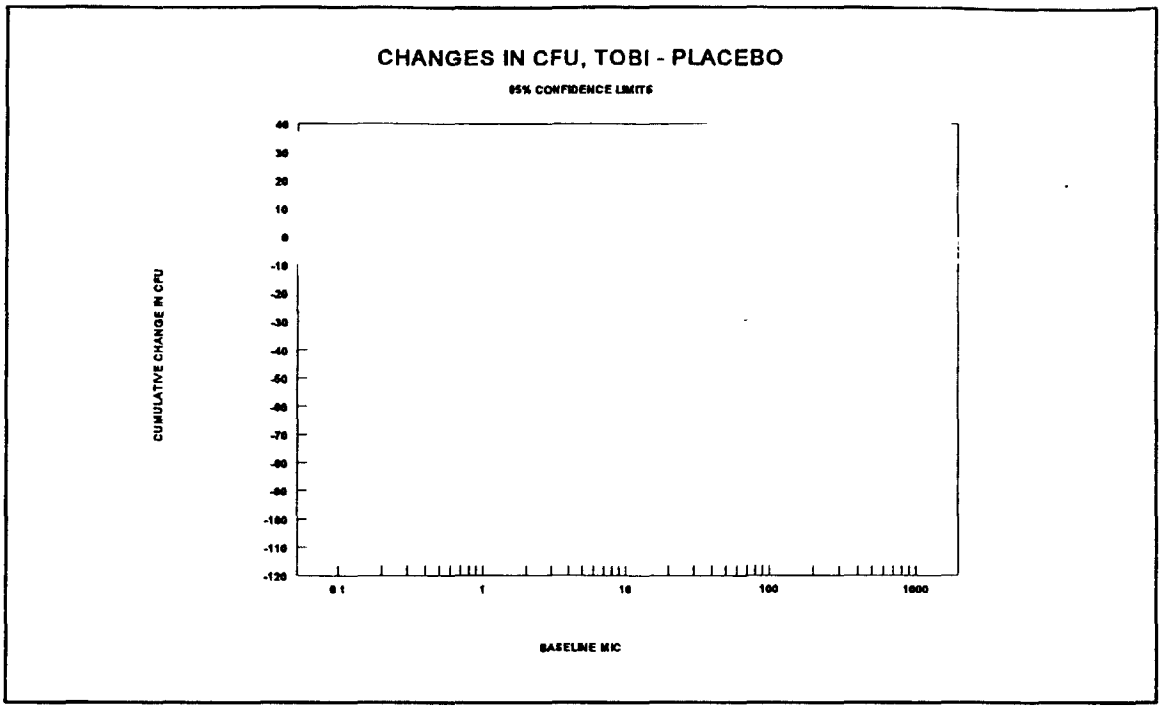


Figure 4.4 I

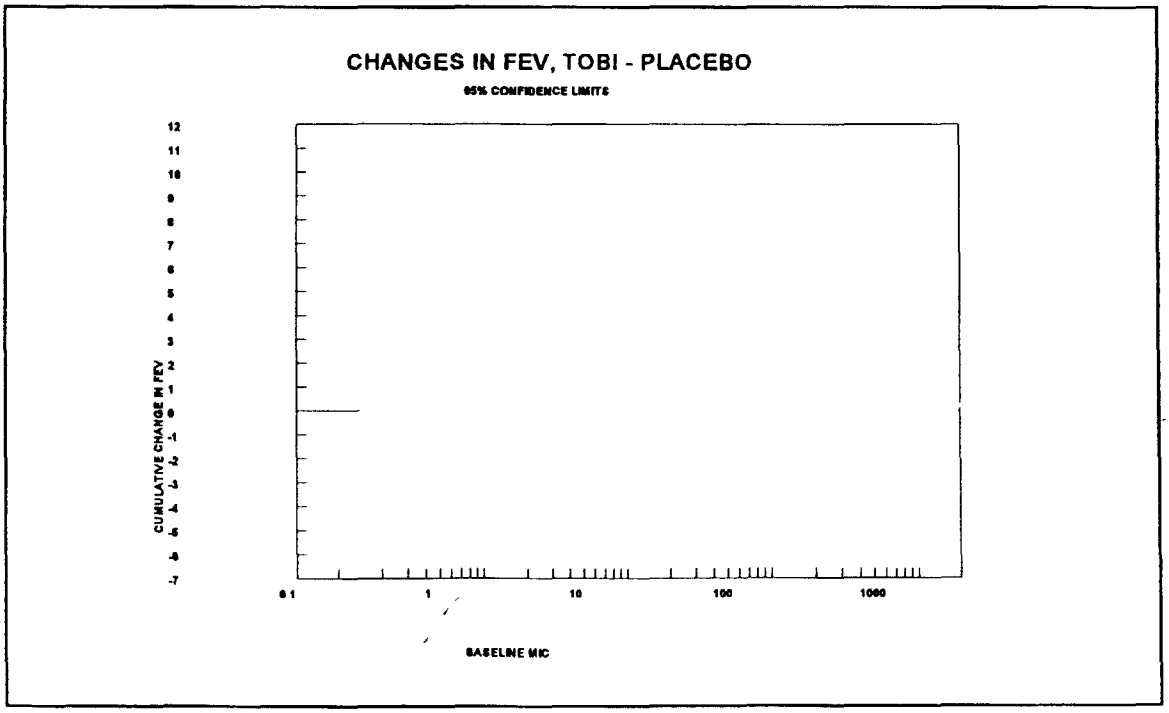


Figure 4.4 ii

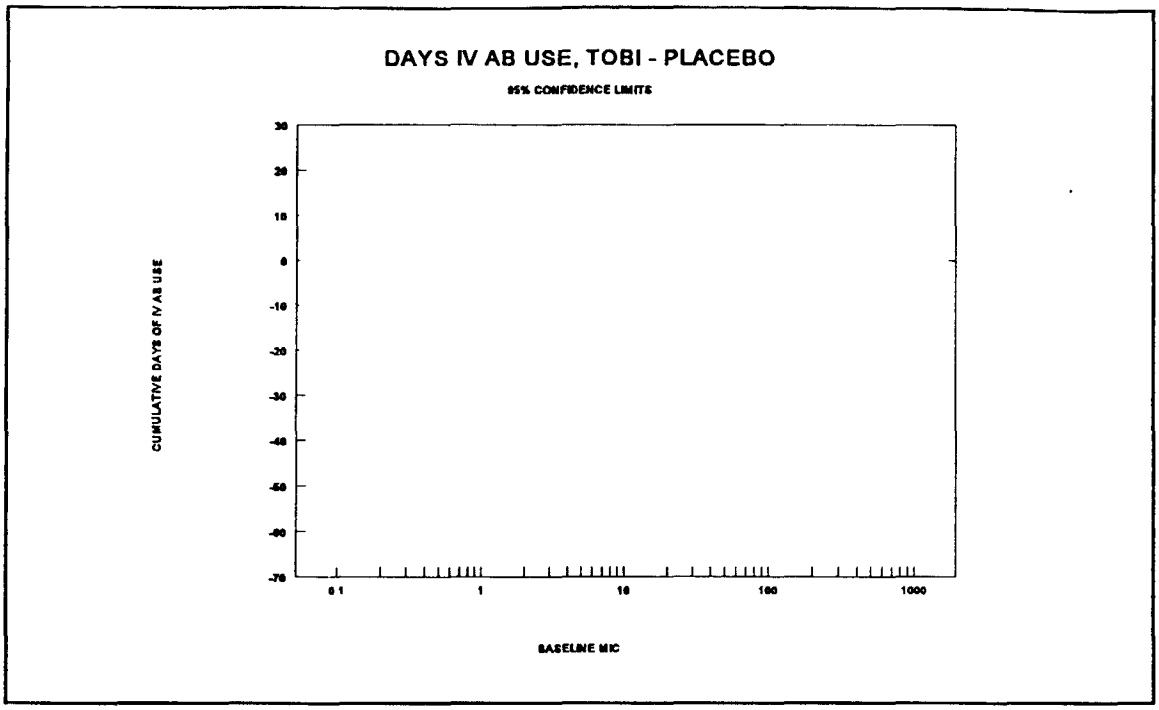


Figure 4.4 iii

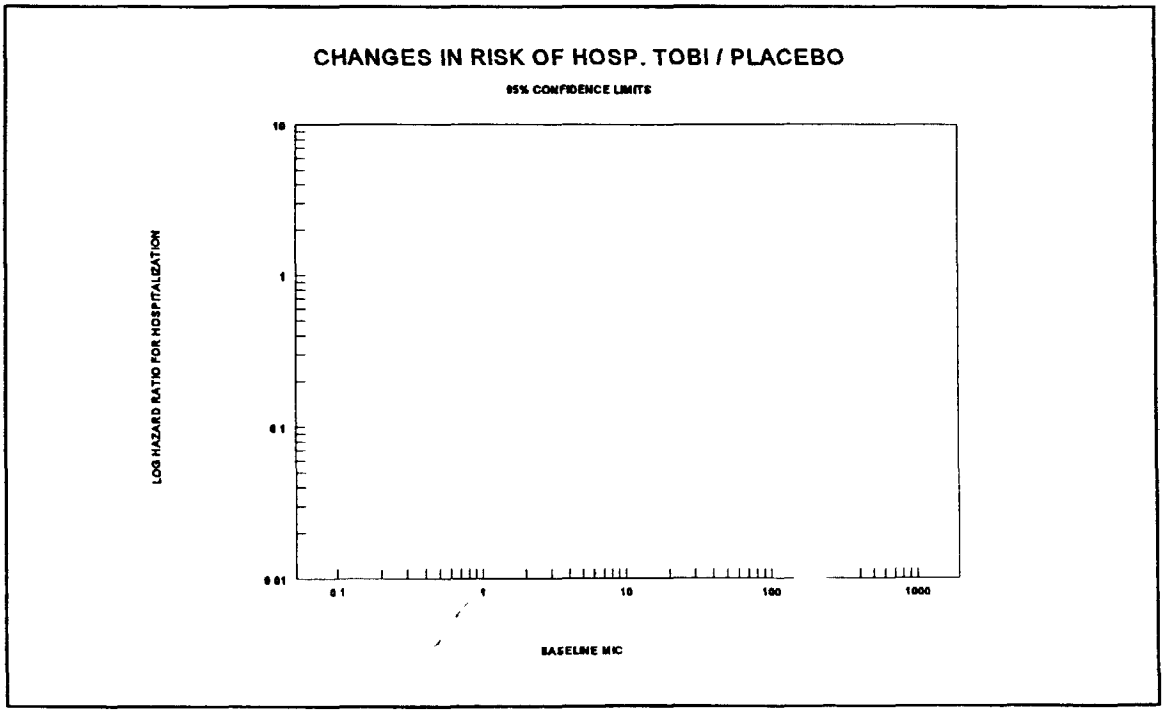


Figure 4.4 iv

Study Conclusions:

Two identical double-blind, placebo controlled trials of CF patients 6 years of age or older colonized with *Pseudomonas aeruginosa* demonstrate a statistically significant increase in FEV_1 in TOBI subjects compared to controls. This increase in FEV_1 is matched by an increase in FVC and decrease in sputum bacterial density. The amount of increase in FEV_1 % predicted is modest, about 11% and 8% in protocol 002 and 003, respectively. It is difficult to relate this increase directly to a clinical benefit, but it does represent a relative increase of 10-20% in their ability to move air. The analyses of secondary outcomes indicated other clinical benefits derived from the use of TOBI. These include delayed time to anti-pseudomonal antibiotic use, fewer days of hospitalization, and fewer days of IV anti-pseudomonal antibiotics. The data did not support a claim for delay in time to hospitalization for lower respiratory tract infection. The difference in results between the two protocols in the secondary outcomes is concerning. However, there is a trend toward statistical significance in the protocol 003 data, and the pooled data show statistically significant results for all except time to hospitalization. Subset analyses were performed, but the studies were not adequately powered to show statistically significant differences in the subgroups. There did seem to be a trend toward greater improvement in FEV_1 in the pediatric and adolescent age groups. There was also a trend toward greater treatment effect on secondary outcomes among the youngest group of subjects (6-12 years) and in females. A series of models studied the impact of the baseline MIC of *Pseudomonas aeruginosa* isolates. There was no apparent decrease in effectiveness of TOBI on change in FEV_1 with increasing MIC. No clear MIC breakpoints for TOBI could be established.

PC-TNDS-004
"An Open-Label Follow-On Trial of Tobramycin for Inhalation in Patients with Cystic Fibrosis"

Objectives: The overall objective of the study was to further document the safety of TOBI when administered as repeated, intermittent, short-term (28 days) therapy in patients with CF who are chronically infected with *P. aeruginosa*.

The primary objectives of the study were:

I. to assess the safety profile of patients receiving intermittent courses of TOBI

II. to assess the incidence of highly tobramycin-resistant (MIC 128 µg/mL) *P. aeruginosa* strains in patients receiving three 28-day courses of intermittent tobramycin solution for inhalation.

(M.O. Comment: The NDA report presented an interim analysis of the safety results obtained on patients who completed Visit 16 (the last day on study drug) or withdrew prior to the NDA data cut-off date of October 15, 1996. The primary purpose of this interim analysis was to provide additional safety data on a group of patients who continued on TOBI for more than six months, and a group who switched from placebo to TOBI at the end of the pivotal trial. The sponsor's focus was on the safety data. The reader is referred to the safety review by Marianne Mann, M.D. for details on this interim analysis. The remainder of this section will give a brief description of the follow-on study and some FEV_1 results.)

Study summary:

This was an open-label, follow-on study for subjects who were enrolled in the two phase III protocols PC-TNDS-002 and PC-TNDS-003. The two inclusion criteria were completion of either protocol 002 or 003 and the ability to comply with the PC-TNDS-004 protocol. The chart on the following page shows the schedule of procedures for the study. Note that the first two visits on the chart are the last two visits of the Phase III trials. The overall design and schedule of visits are similar to those of the phase III trials.

Schedule of Procedures

Visit	10[1]	11[2]	12	13	14	15	16	17
Treatment		Start	End	Start	End	Start	End	
Week	20	24	28	32	36	40	44	48
Day	140 ± 4	168 ± 4	196 ± 4	224 ± 4	252 ± 4	280 ± 4	308 ± 4	336 ± 4
Informed Consent	X							
Clinical Evaluation and Patient History	X	X	X	X	X	X	X	X
Complete Physical Examination	X	X[3]					X	X[3]
Chest X-ray	X	X[3]					X	
Sputum Specimen[4]	X	X		X		X	X	X
Safety Laboratories	X	X		X		X	X	X[3]
Serum Pregnancy Test		X		X		X	X	
Urine Proteinuria[5]	X	X		X		X	X	X[3]
Spirometry								
Pre-Dose	X	X	X	X	X	X	X	X
30 minutes Post	X	X[6]					X	
Audiology[7]	X						X	
Study Drug								
Dispensed		X		X		X		
Accountability	X		X		X		X	

[1] Data to be obtained from Visit 10 of PC-TNDS-002 or PC-TNDS-003

[2] Data to be obtained from Visit 11 of PC-TNDS-002 or PC-TNDS-003. Hematology, serum chemistries, and urine analysis must have been completed at this visit for patients to continue on the follow-on protocol.

[3] If findings at previous visit were abnormal, procedures were repeated.

[4] If patient was unable to expectorate a sputum specimen, a throat swab was obtained.

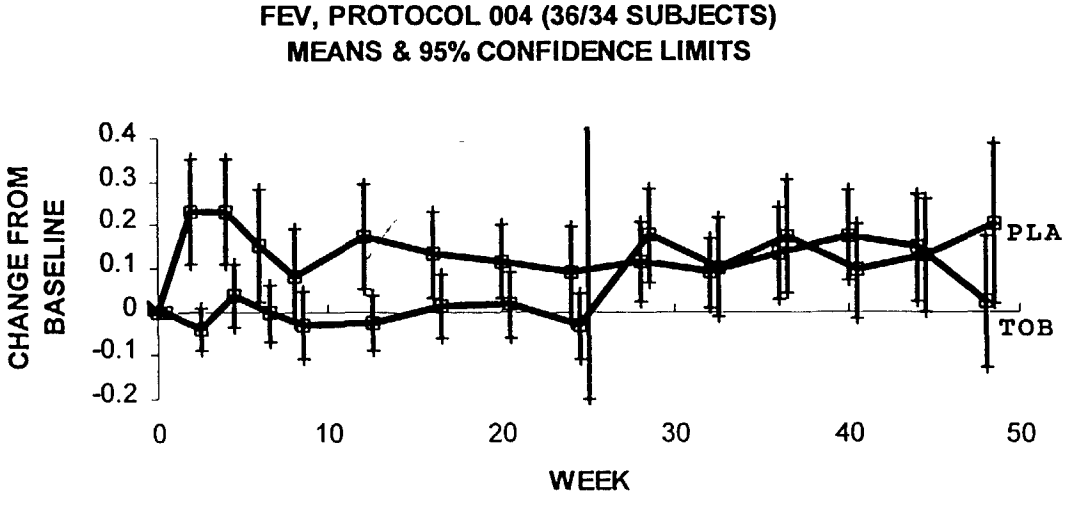
[5] Urine analysis for proteinuria testing was performed prior to each cycle of drug administration, *i e* , every eight weeks

[6] At Visit 11, post-dose spirometry was performed only on patients continuing in the follow-on protocol.

[7] Audiology was conducted only at selected study sites at study initiation and at the conclusion of the last 28-day treatment period

The important differences to note between this trial and the pivotal trials are the open-label design and the methodology of sputum culture. Patients who are enrolled in this trial received TOBI regardless of whether they received TOBI or placebo in the clinical trials. Since all enrolled subjects receive active drug, the study adds little efficacy information to the NDA package. This is consistent with its major objectives of increasing information on safety. The other important difference with this trial is that quantitative sputum cultures were not done in this trial. The usual semi-quantitative methods used in most clinical laboratories for sputum bacteriology were used in this trial. Unfortunately, this trial does not provide the means to answer one of the questions left from the pivotal studies. In those protocols, there was a decrease in the treatment effect on bacterial sputum density in successive cycles. This effect can not be followed into this protocol. Information on MIC's of *Pseudomonas aeruginosa* is still available. The other limitation of the data provided in the NDA is that only a small number of subjects had completed or withdrawn from protocol 004 in time for the NDA submission. This interim report included 36 subjects who had received TOBI and 34 subjects who had received placebo in either protocol 002 or 003.

Conclusions: The following graph shows the FEV_1 vs. week for subjects enrolled in the follow on study. The first 24 weeks are data from protocol 002 or 003. It appears that those subjects who received placebo have an increase in FEV_1 that is similar to the increase seen in TOBI subjects in the pivotal trial.



The implication of this finding is that patients who are treatment naive can show similar increases in FEV_1. The question that remains is the optimal timing of use of aerosolized tobramycin, and whether continued use of TOBI is required to sustain this FEV_1 increase. There may be different drug treatment schedules that will provide optimal effect and minimize the development of resistance. However, these trials were not designed to address these questions.

SUMMARY OF SAFETY

Please see the safety review by Marianne Mann, M.D., for the complete safety review. The following summarizes the conclusions of that review. Three separate issues were outlined.

Voice Alteration: Reports of voice alteration were more common in TOBI patients than in the placebo group. These episodes were transient in nature and episodic. None of the subjects were noted with permanent voice alteration. This finding is similar to voice alterations that occur with DNAse therapy.

Cochlear Toxicity: Tinnitus was the sole manifestation of cochlear toxicity in these studies. Sixteen episodes of tinnitus were reported in 8 TOBI patients versus none in the placebo patients. There was concern expressed by the safety reviewer that tinnitus may be a harbinger of cochlear toxicity with continued use.

Changes in MIC for *Pseudomonas aeruginosa* Isolates: Upward shifts in MIC for *Pseudomonas aeruginosa* isolates were noted in the TOBI group as compared to placebo over the time of the pivotal studies. The clinical significance of this upward shift is unclear. The review did show that "subjects who withdrew prematurely often had resistant infections as a potential contributing factor". The changes in MIC over time may ultimately result in greater prevalence of resistant *Pseudomonas aeruginosa* isolates in patients with CF and decreased effectiveness of TOBI. Alternatively, it was suggested that the *Pseudomonas aeruginosa* isolates with high MIC's may be less virulent. However, no data to support this theory are provided by the sponsor.

CONCLUSIONS

In the pivotal trials, PC-TNDS-002 and PC-TNDS-003, the use of TOBI resulted in an increase in mean FEV_1 and FVC compared to subjects receiving placebo. A statistically significant difference in time to first use of anti-pseudomonal antibiotics was shown for TOBI patients compared to placebo. In addition, the sponsor was able to show that CF patients who received TOBI required fewer days of anti-pseudomonal antibiotic use and fewer hospital days. The sponsor was not able to demonstrate a difference in time to hospitalization for lower respiratory tract infections.

The sponsor has submitted data that demonstrate clinical benefit for cystic fibrosis patients colonized with *Pseudomonas aeruginosa*. Some potentially significant adverse reactions were identified in the safety review. Of great concern is the potential for ototoxicity with chronic use and the upward shifts in MIC for *Pseudomonas aeruginosa* isolates. The pivotal trials were designed to study the use of TOBI over a six month period, but it is recognized that TOBI is likely to be used for longer periods of time once approved. Voice alteration was also identified as a transient, minor side effect of the use of TOBI.

PHASE IV STUDIES

The following phase IV commitments for further clinical study were made by agreement of the sponsor and the division.

LABELING CHANGES

The package insert submitted on July 10, 1997 was not acceptable because it included statements regarding decrease in hospitalization which were not supported by the data. This and other labeling issues were addressed in labeling submissions dated Oct. 16, 1997 and Dec. 17, 1997. A final version of the label was agreed to by the division and the sponsor at a meeting on Dec. 22, 1997. The final version of the package insert was submitted on Dec. 22, 1997. A copy of this package insert is given in the appendix.

RECOMMENDATIONS

Based on the results of the pivotal studies, the phase IV commitments made by the sponsor, and the labeling changes agreed to by the division and the sponsor, the medical officer recommends approval of TOBI for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. This recommendation is limited to CF patients who are 6 years of age or older, and whose FEV_1 %predicted is between 25% and 75%. TOBI is not recommended for CF patients with *Burkholderia cepacia*.

/S/

John Alexander, M.D.

CC:
Original NDA 50-753
HFD-520
HFD-520/MO/Alexander
HFD-520/SMO/Soreth
HFD-520/CSO/Duvall-Miller
HFD-520/Chem/Pagay
HFD-520/Micro/King
HFD-520/Pharm/Ellis
HFD-590/MO/Mann
HFD-725/Stats/Hammerstrom
HFD-880/Biopharm/Zheng

Concurrence:
HFD-520/SMO/Soreth 8/11/98
HFD-520/DivDir/Chikami 8/12/98

NDA #50-753
Inhaled Tobramycin for Cystic Fibrosis Patients
Safety Review

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NDA #50-753
Safety Review of NDA
By: Marianne Mann, Medical Officer, DSPIDP MM/a MD 2/10/98

I. Introduction
This safety review refers to NDA #50-753. Please refer to the efficacy review of NDA #50-753 by John Alexander for information regarding efficacy.

The safety database for inhaled tobramycin (TOBI) in the treatment of cystic fibrosis involves the following studies:

PC-TNDS-001: A pharmacokinetic study of inhaled TOBI using three different nebulizer systems in patients with cystic fibrosis.
PC-TNDS-002: 109 TOBI patients (300 mg bid for 24 weeks) and 114 placebo patients
PC-TNDS-003: 149 TOBI patients (300 mg bid for 24 weeks) and 148 placebo patients
PC-TNDS-004: Open-Label Follow-up: 68 TOBI patients from -002 or -003 above
Ramsey Study: 36 TOBI patients (600 mg t.i.d. for 4 weeks) and 35 TOBI patients (600 mg t.i.d. for 8 weeks)

This safety review begins with a brief overview of the pharmacokinetic results and tolerability of TOBI from PC-TNDS-001. The review then focuses on the combined data from PC-TNDS-002 and PC-TNDS-003, the two identical pivotal randomized trials which were submitted in support of this indication. Safety data from these two trials will be combined since the trials were identical. Finally, a review of the safety data available for the 68 patients enrolled in the open-label TOBI study PC-TNDS-004 will follow, since it provides important information about the safety of TOBI when given for longer than 6 months. The Ramsey study will not be reviewed since the dosing of TOBI in this study is not the indicated dose for this application, and since complete case reports from this study are not available for FDA review.

II. Safety Review of PC-TNDS-001: A Pharmacokinetic Study of TOBI
This study, entitled "A Phase II Clinical Trial to Compare Safety, Efficacy, and Pharmacokinetics of an Aminoglycoside (Tobramycin) Formulation Administered by Three Different Nebulizer Delivery Systems to Patients with Cystic Fibrosis" was performed from July 7 to October 10, 1994 at 10 U.S. sites. Patients received, in random order, one administration of 300 mg TOBI from each of three nebulizer delivery systems: UltraNeb (n=64 patients), Sidestream (n=62 patients), and Pari LC (n=65 patients). Effectiveness was based on sputum drug concentration, which was assessed 10 minutes following aerosolization.

Results demonstrated that two of the nebulizer systems (Pari LC and Sidestream) achieved tobramycin concentrations of $\geq$ 128 µg/g of sputum in 87% of the patients. There were few adverse events, and all three nebulizers were safe and well-tolerated. Mean peak serum concentrations were 0.57 ± 0.38 µg/ml using the Pari LC nebulizer and were 0.74 ± 0.43 µg/ml using the Sidestream nebulizer.

Medical Officer Comment:
1. While the results of PC-TNDS-001 are encouraging regarding the tolerability of TOBI and the relatively low mean serum concentrations, a different nebulizer (the modified Pari LC) was utilized in the Phase III trials (PC-TNDS-002 and PC-TNDS-003). Therefore, PC-TNDS-001 data regarding pharmacokinetics, safety, and tolerability are not relevant to the Phase III trials and to the nebulizer system which will be used pending product approval.

III. Safety Review of PC-TNDS-002/-003: The Pivotal Parallel Group Studies
III.A. Exposure to TOBI
Patients received up to 3 cycles of treatment in the parallel group studies. Each cycle consisted of 28 days on-drug, and 28 days off-drug. Exposure of patients to TOBI is described in the following table:

Patient Exposure to TOBI: Parallel Group Studies

	1 Cycle on TOBI	2 Cycles on TOBI	3 Cycles on TOBI
# of patients	253	242	233*
mean dose (mg) of inhaled TOBI per cycle	15,917	15,361	15,579
mean duration of treatment (days) per cycle	27	26	26

*232 of these 233 patients completed all three cycles of TOBI

Medical Officer Comments:
1. It is notable that 232 of 258 TOBI patients (90%) completed all 3 cycles of treatment. This suggests that, overall, TOBI was well tolerated.

2. The true extent of exposure to TOBI is very difficult to measure due to variations in aerosol characteristics, in individual ventilatory patterns of distribution, and in the extent of systemic absorption of drug.

III.B. Patient Disposition
Patient disposition is described below:

Patient Disposition
Parallel Group Studies

	TOBI	Placebo	Total
# Enrolled	258	262	520
# Completed	232 (89.9%)	232 (88.5%)	464 (89.2%)
# Withdrawn	26 (10.1%)	30 (11.5%)	56 (10.8%)

FDA analysis of reasons for study drug withdrawal are given in section III.I. of this review. A large percentage of patients in each arm completed the entire 6 month study, suggesting that study drug was well tolerated.

III.C. Extent of Systemic Absorption of TOBI

Patients in the phase III trials used a modified Pari LC nebulizer (Pari LC Plus), a system selected to improved delivery of tobramycin. In this study, with a new group of cystic fibrosis patients, tobramycin was administered at the same dose (300 mg) and formulation as used in PC-TNDS-001.

Results from the phase III trials indicate that the modified Pari LC Plus system nearly doubled the delivery of tobramycin to the lungs and in serum. Mean peak sputum concentrations were 1199.2 µg/g and mean peak serum concentrations were 1.00 µg/mL in this study. Serum levels in the phase III trials ranged from below limits of quantitation to µg/ml. Safe serum trough levels following parenteral therapy are generally defined as µg/ml. and 94% of patients randomized to receive TOBI had serum levels of tobramycin below this conservative cutoff for toxicity.

Medical Officer Comment:

1. The systemic absorption of TOBI was minimal in the phase III clinical trials, however the duration of exposure is prolonged. Safety concerns, therefore, will include the more common toxicities (i.e. ototoxicity, nephrotoxicity, and neurotoxicity) associated with the aminoglycosides as a class.

III.D. All Adverse Events

A summary of all adverse events for 258 TOBI patients and 262 placebo patients as provided by the sponsor showed a statistically significant difference for the following adverse events:

Sponsor's Analysis
All Adverse Events By Preferred Term
Parallel Group Studies

Adverse Event	TOBI (n=258)	Placebo (n=262)	p-value by Fisher's Exact Test
fever	38.8% of patients had 168 episodes of fever	50.8% of patients had 235 episodes of fever	0.006
abdominal pain	17.4% of patients had 79 episodes of abdominal pain	31.3% of patients had 124 episodes of abdominal pain	<0.001
anorexia	22.5% of patients had 79 episodes of anorexia	35.1% of patients had 134 episodes of anorexia	0.002
vomiting	14.7% of patients had 54 episodes of vomiting	24.8% of patients had 106 episodes of vomiting	0.004
voice alteration	13.2% of patients had 58 episodes of voice alteration	6.5% of patients had 20 episodes of voice alteration	0.012
hyperventilation	6.2% of patients had 17 episodes of hyperventilation	12.2% of patients had 36 episodes of hyperventilation	0.022
tinnitus	3.1% of patients had 16 episodes of tinnitus	0 patients	0.003

Medical Officer Comments:

1. Fever, abdominal pain, anorexia, vomiting, and hyperventilation occurred less commonly in the TOBI arm. While some of these results may be a chance finding which can occur following multiple statistical analyses, the lower frequency of digestive system complaints of anorexia and vomiting in the TOBI arm appear consistently across several analyses. In addition, there is a potential mechanism (i.e. absorption of antibiotic to the GI tract with a potential effect on local flora) to support this finding. It is also noteworthy that diarrhea occurred with comparable frequencies in the TOBI and placebo arms. Therefore, if TOBI affected local flora it did not result in an increased incidence of diarrhea.

2. Voice alteration was approximately twice as common in the TOBI arm and this was statistically significant.

3. Tinnitus was significantly more common in the TOBI arm, occurring in 3.1% of TOBI patients versus no placebo patients. Tinnitus may be a manifestation of the known ototoxicity associated with tobramycin and is discussed in greater detail in Section III.J.(2) of this safety review.

III.E. Treatment Emergent Adverse Events

The analysis by preferred term of treatment-emergent adverse events showed the following statistically significant differences between TOBI and placebo patients:

Sponsor's Analysis
Treatment Emergent Adverse Events By Preferred Term
Parallel Group Studies

Adverse Event	TOBI (n=258)	Placebo (n=262)	p-value by Fisher's Exact Test
fever	32.9% of patients had 149 episodes of fever	43.5% of patients had 190 episodes of fever	0.015
abdominal pain	12.8% of patients had 55 episodes of abdominal pain	23.7% of patients had 89 episodes of abdominal pain	0.001
anorexia	18.6% of patients had 65 episodes of anorexia	27.9% of patients had 102 episodes of anorexia	0.013
vomiting	14.0% of patients had 48 episodes of vomiting	22.1% of patients had 88 episodes of vomiting	0.017
voice alteration	12.8% of patients had 56 episodes of voice alteration	6.5% of patients had 20 episodes of voice alteration	0.017
tinnitus	3.1% of patients had 16 episodes of tinnitus	0 patients	0.003

Medical Officer Comment:
1. Significant findings regarding an analysis of treatment emergent adverse events include a lower incidence of fever, abdominal pain, anorexia and vomiting in the TOBI arm, and higher incidence of voice alteration and tinnitus in the TOBI arm. Voice alteration not only occurred with greater frequency in the TOBI arm, but the cases which occurred were more severe in nature.

III.F. Adverse Events Attributed to Study Drug
Drug-related adverse events were those judged by the investigator to be remotely, possibly, probably, or definitely related to study drug. Drug-related adverse experiences occurred in 121 of 258 (46.9%) TOBI patients and 125 of 262 (47.7%) placebo patients. The most common adverse experiences were pulmonary in nature (cough, pharyngitis, rhinitis, chest pain, hemoptysis, and increased sputum), and occurred with comparable frequency between study arms. Taste perversion also occurred with almost equal frequency between arms (6.2 and 6.1% of TOBI and placebo patients, respectively). The only adverse event which occurred significantly more frequently in any treatment arm was dyspnea, which occurred in 8.8% of placebo patients versus 4.3% of TOBI patients.

III.G. Adverse Events On-Drug and Off-Drug
Patients received up to 3 cycles of treatment in the parallel group studies. Each cycle consisted of 28 days on-drug, and 28 days off-drug. A review of adverse events on TOBI versus off TOBI revealed that the majority of respiratory and gastrointestinal symptoms occurred with equal

frequency regardless of the phase of treatment.

Pharyngitis occurred in 28.7% of TOBI patients during the on-drug period versus 17.1% of the off-drug period, but this same finding was noted in the placebo arm where pharyngitis occurred in 28.6% of patients on-drug versus 17.6% of those off-drug. Thus, pharyngitis occurred more frequently during TOBI treatments, but may be an effect of nebulizer therapy rather than attributed to TOBI, per se. Taste perversion also followed this same pattern, and may also simply be an effect of nebulizer therapy.

Voice alteration not only occurred with greater frequency in the TOBI arm, but was more common during the on-drug period of the study (11.6% on-drug versus 2.7% off-drug). Voice alteration was less common in the placebo arm, but when it occurred it was more common during the on-drug phase of the study (4.2% on-drug versus 2.7% off-drug). Thus, voice alteration may in part be attributed in part to nebulizer treatments, but is also attributed to inhaled tobramycin therapy.

III.H. Serious Adverse Events

There were 4 deaths in the parallel studies; all occurred in the placebo arm. Two deaths occurred while on study, while one withdrew from the study and subsequently died, and the final patient died after completing the study.

Narratives of serious adverse events which required hospitalization were supplied by the sponsor were reviewed by FDA. A total of 120 placebo patients had 199 serious adverse events compared to 96 TOBI patients who had 130 serious adverse events. The following table describes the serious adverse events:

FDA Analysis: Serious Adverse Events Requiring Hospitalization

	TOBI	Placebo
Number of Patients Experiencing a SAE	96	120
Total Number of SAEs	130	199
Pulmonary Exacerbations	105	163
Pulmonary Exacerbations with Sinusitis	6	5
Pneumothoraces	1	5
Sinusitis Exacerbations	5	6
Gastrointestinal Symptoms or Disease	5	8
Elective surgeries for line placement, G-tube, etc	4	7
Deaths	0	1
Miscellaneous	4	4
Total Number of Patient-Days in Hospital for SAE Management	1283	2046

In addition there were 6 patients who had serious adverse events not related to hospitalization: five placebo patients had chest pain, laser eye surgery, mediport insertion, increased cough, and hyperkalemia and one TOBI patient had pharyngitis.

Medical Officer Comment: *This analysis reveals that the large majority of serious adverse events in both treatment arms were pulmonary exacerbations requiring hospitalization. Notably, a greater number of placebo patients experienced a greater number of serious adverse events, which may reflect the efficacy of the TOBI in preventing pulmonary exacerbations. There is certainly no evidence that patients randomized to TOBI had any specific type of serious adverse event more often than placebo.*

III.I. Adverse Events Leading to Study Withdrawal

FDA analyzed the mean and median time from visit 3 to study withdrawal, and categorized the reason for study withdrawal in TOBI and placebo patients as demonstrated below:

FDA Analysis
Time from Visit 3 to Study Withdrawal and
Reason for Premature Study Withdrawal

	TOBI (n=26 subjects)	Placebo (n=30 subjects)
Mean time from V.3 to Study Withdrawal	62.2 days	56.4 days
Median time from V.3 to Study Withdrawal	57 days	56.5 days
Reason for Withdrawal From Study		
Adverse Event	8 (30.8%)	7 (23.3%)
Deterioration in Pulmonary Status	5 (19.2%)	14 (46.7%)
Loss to Follow-up	5 (19.2%)	3 (10%)
Noncompliance	3 (11.5%)	3 (10%)
Protocol Violation	3 (11.5%)	0
Pregnancy	1 (3.8%)	0
Resistant Pseudomonas	1 (3.8%)	0
Patient Wished to Stop Study	0	2 (6.7%)
Death	0	1 (3.3%)

Medical Officer Comments:

1. Comparable numbers of TOBI and placebo patients withdrew from the study due to adverse events. Tolerability of TOBI according to this analysis appears comparable to placebo.

2. Almost three times as many placebo patients withdrew from the study due to deteriorations in pulmonary status, suggesting that TOBI may have beneficial clinical effects. One patient in the TOBI arm, however, withdrew prematurely from the randomized trial due to the development of a resistant pseudomonas infection requiring intravenous therapy and inhaled colistin. The development of resistant infections is a concern with TOBI and will be explored in this safety review in Section III.N.

III.J. Organ Specific Adverse Events of Interest

III.J. (1). Bronchospasm

Spirometry was obtained immediately before and 30 minutes after the nebulized dose of study drug at visits 3, 10, 11, and 16 to determine whether study drug induces bronchospasm. In the parallel group studies, the median change in FEV-1 measured 30 minutes after study drug treatment was -1.77% for the TOBI group and -2.62% for the placebo group at visit 3. At visit 10, these results were -2.00% and -2.01% for the TOBI and placebo groups, respectively. Thus, overall, the median change in FEV-1 pre and post nebulizer treatment did not appear to change significantly in either TOBI or placebo patients.

Medical Officer Comment:

1. Median changes in FEV-1 pre- and post- study drug administration did not change significantly, however this analysis may not detect a small but significant number of patients who may have reacted to TOBI with acute bronchoconstriction. Therefore, FDA analyzed the relative number of patients in each treatment arm who had a $\geq$ 15% fall in FEV-1 following study drug

administration.

FDA Analysis of Bronchospasm Pre and Post Study Drug Therapy
at Visits 3, 10, and 16

	Inhaled TOBI Solution (n=258)	Inhaled Placebo Solution (n=262)
Number of Patients with ≥ 15 % fall in FEV-1 post treatment	22	20
Percentage of Patients with ≥ 15% fall in FEV-1 post treatment	8.5%	7.6%

Medical Officer Comment:

1. The number and relative percentage of patients with bronchospasm (defined as a ≥ 15% fall in FEV-1 post treatment with study drug) was comparable in the TOBI and placebo arms, and only involved approximately 8% of all subjects. Bronchospasm can occur following TOBI treatments, therefore, but it probably results from the nebulizer treatment and not to tobramycin, per se.

III.J. (2). Ototoxicity

Deafness:

Seven patients reported deafness: 4 TOBI and 3 placebo patients. The 4 TOBI patients had transient decreases in hearing which were mild to moderate in severity; audiology exams were performed in three of these patients and did not reveal ototoxicity. Two of the 4 TOBI patients with deafness had other causes identified (otitis media in one, rock concert in another). Serum tobramycin levels were below 2 µg/mL in all 4 patients, and all reported normal hearing by the end of the study.

Audiology Evaluations:

Audiology testing was performed in 302 patients. The criterion for an ototoxic effect in these study protocols was a bilateral, high-frequency 15 dB or greater decrease in hearing at two consecutive frequencies, when comparing baseline audiogram to final audiogram. There were no patients in the parallel group studies who had bilateral results with a ≥ 15 dB decrease at any two consecutive octave frequencies at the last visit.

Medical Officer Comment:

1. The definition of ototoxicity used in the study was a 15 db hearing loss in at least 2 consecutive frequencies in both ears. The sponsor therefore provided another analysis of ototoxicity using the FDA's more sensitive definition for ototoxicity:

- *A 10 db hearing loss in at least three consecutive frequencies in either ear OR*
- *A 15 db hearing loss in at least two consecutive frequencies in either ear OR*
- *A 20 db hearing loss at any frequency in either ear*

The results of this analysis were that six patients in the TOBI group (4.1%) and 10 patients in the placebo group (6.5%) had ototoxicity. There does not appear to be any greater tendency for ototoxicity with TOBI versus placebo, even using these more sensitive audiometric criteria.

Tinnitus:

Eight patients, all in the TOBI group, reported a total of 16 episodes of tinnitus. No placebo patients reported tinnitus. A summary of the 8 patients with tinnitus follows:

Patients with Tinnitus: Summary of 8 cases

Age/Sex	Description/Severity	Duration in Days	Ototoxicity present?	Comments
31/F	Tinnitus Right ear/Mild at end of first cycle on tx	1	No	Concurrent AE's included cough, chest and nasal congestion, headache, and dyspnea
27/F	Ringing in Ear/Mild during cycle 2 on tx	10	No	Concurrent AE's included multiple respiratory complaints
18/F	Ears Ringing/Moderate during cycle 1 on tx	1	No	Concurrent AE's included nausea, dizzy, passed out, mouth burning: all occurred on same day with one day duration.
31/F	Tinnitus/Mild after first cycle off tx	6	No	Concurrent AE's included fatigue, increased cough, headaches, and sorethroat. Patient on daily ibuprofen.
29/M	Ringing in ears/Mild at end of first cycle on tx Ringing in ears/Moderate at end of first cycle off tx Ringing in ears/Mild at end of first cycle off tx leading into cycle 2 on tx	22 1 40	Not done	3 separate AE's but one continuous episode of tinnitus lasting 63 days.
28/F	Ringing in Ears/Mild during cycle 1 on tx Ringing in Ears/Mild during cycle 1 on tx	4 2	No	Concurrent AE's included hoarse voice, fatigue. Patient on daily ibuoprofen.
15/F	Ringing in R Ear/Mild during cycle 1 on tx Ringing in Ears/Moderate after cycle 2 off tx Ringing in Ear/Mild during cycle 3 on tx Ringing in Ear/Mild during cycle 3 on tx Ringing in Ear/Mild during cycle 3 on tx	2 3 2 2 2	No	Patient has history recurrent otitis media.
25/M	Tinnitus Both ears/Mild	3	No	Patient on concurrent IV tobramycin.

Medical Officer Comments:
1. Tinnitus appears to truly be more common in the TOBI patients. It is particularly concerning that many patients experienced multiple episodes of tinnitus. Tinnitus is one of the earliest manifestations of cochlear toxicity.

2. Standard audiometric evaluations used in the trials tested to 8000 Hz and were normal in the patients with tinnitus, but testing was not performed at the time of the event. In addition, these evaluations may not detect higher frequency hearing loss (>8000 Hz) which might occur with tinnitus.

3. There is no apparent relationship between the development of tinnitus and duration of TOBI treatment, since many episodes occurred during the first cycle of therapy. Thirteen of the 16 episodes occurred while "on" TOBI, however.

4. A pharmacodynamic relationship between tinnitus and TOBI serum concentrations is difficult to discern since TOBI serum levels were not obtained at the time of the adverse event of tinnitus. Nonetheless, the available serum tobramycin levels obtained routinely in these 8 subjects exceeded 1 ug/mL in only two subjects, and no patients exceeded 2 ug/ml.

III.J.3. Vestibular Toxicity

Dizziness:

Twenty TOBI and twenty placebo patients experienced dizziness. Fifteen of the 20 TOBI patients were evaluated for audiology and none reported ototoxicity. All episodes of dizziness in the TOBI arm were transient, and most lasted less than a week in duration.

Vestibular Disorder:

Only one patient in the trial (TOBI arm) experienced a vestibular disorder. This patient was a 35 year old female who experienced viral labrynthitis of mild severity which resolved within approximately 16 days without specific therapy.

Medical Officer Comment: *Vestibular toxicity was very rare in this trial, and did not appear to occur with any greater frequency or severity in the TOBI patients compared to placebo.*

III.J.4. Neurotoxicity/Paresthesia

Five TOBI and 2 placebo patients reported paresthesia during the study. The five cases of paresthesia in the TOBI arm are summarized below:

TOBI Patients with Paresthesia: Summary of 5 Cases

Age/Sex	Description/Severity	Duration in Days	Comment
25/M	bilateral leg numbness/moderate	1	Concurrent AE's included blurred vision, nausea, and severe episode of coughing
15/F	throat tingling during study drug treatment/mild	3	Concurrent AE's included runny stuffy nose, sinus tenderness, head cold, and coughing during study drug treatment
14/F	numbness right toe/moderate	14	Patient recovered spontaneously
13/F	numbness left side/mild numbness right side/mild	1 1	Concurrently had hip and back pain due to spondylolisthesis Hospitalized for G-E reflux 6 days before this event
22/F	numbness of arms and legs/mild numbness of legs/mild numbness of arms and legs/mild and intermittent	1 1 27	spontaneous recovery concurrent AE's included fever, nausea, abdominal cramps concurrent AE's included difficulty breathing, light-headedness, sore throat, headache, fatigue, and increased neck, joint and back pain

Medical Officers Comment:

1. Paresthesias occurred with slightly greater frequency in the TOBI arm when compared to placebo (5 TOBI versus 2 placebo patients). The five cases which occurred in the TOBI arm were generally of short duration and may have been related to other concomitant conditions. It is difficult to attribute the cases of paresthesia directly to TOBI as a cause.

III.K. Adverse Event by Age and Gender

Subgroup analyses were performed for three age categories: children age 6 to 12, adolescents age 13-18, and adults over age 18. Overall, the adverse experience profiles were similar within age groups. Of the 8 cases of tinnitus, however, seven occurred in adults, and one in an adolescent. Voice alteration also tended to occur somewhat more often in older subjects. Subgroup analyses by gender revealed no particular differences in adverse events between males and females.

III.L. Pregnancy

One TOBI patient became pregnant during the study. This 28 year old had completed one cycle of TOBI before withdrawing due to her pregnancy. Continued clinical evaluations did not demonstrate any complications and she delivered a healthy baby girl at term.

III.M. Clinical Laboratory Evaluations

Renal Function:

In the TOBI group, the increases in mean BUN value at each visit over baseline were slightly greater and more consistent than the increases observed in the placebo group. Overall, however, the mean values for BUN in the TOBI arm varied from 12.27 (visit 3) to 13.01 mg/dL (visit 10), which is not a clinically relevant change overall. A comparable number of patients (21 TOBI

and 19 placebo) in each arm had a doubling of BUN from baseline, and only 4 patients in the TOBI group and 2 in the placebo arm had BUN values that increased to levels between 20-30 mg/dL. Thus, there is no evidence of clinically significant renal toxicity from the evaluation of serum BUN levels.

There was little variation in mean serum creatinine values in either the TOBI or placebo arms. Of the 520 patients enrolled in the parallel group studies, no patient had an increase of 1 mg/dL at the last study visit. Only 18 patients (9 from each arm) had a serum creatinine value $\geq$ 50% compared to baseline during the study. These elevated creatinine levels were sporadic with no apparent association with TOBI on and off cycles. All these values were reversible, and dropped at the subsequent visit in all except one patient; the visit 10 values returned to visit 3 baseline values in most cases. A summary of the TOBI patients with elevations in serum creatinine elevations $\geq$ 50% from baseline follows:

TOBI Patients with Elevations in Serum Creatinine $\geq$ 50% of Baseline Values

Patient age/sex	Baseline Creatinine (mg/dL)	Maximum Creatinine (mg/dL) During Study and Visit Detected	Outcome Summarized
8/F	0.6	0.9 at Visit 5	Patient had no AE's, no hospitalizations, no IV tobramycin given. Final creatinine was 0.8 mg/dL at visit 11.
11/M	0.6	0.9 at Visit 5 and again at Visit 15	Patient had 2 episodes with no IV tobramycin given. Final creatinine was 0.6 at Visit 16
15/F	0.6	1.0 at Visit 5	Patient withdrawn from study for using aerosolized tobramycin during the study. Final creatinine was 0.7 at withdrawal.
14/F	0.6	0.9 at Visit 9	Patient had concurrent AE of arthralgia. Final creatinine was 0.8 at visit 10.
28/M	1.1	1.7 at Visit 11	Patient had concurrent AE of weight loss and congestion. Final creatinine was 1.2 at Visit 13.
18/F	0.7	1.3 at Visit 9	Hospitalized for pulmonary exacerbation and eating disorder and began IV tobramycin on same day as elevated creatinine. Final creatinine was 0.7 at Visit 10.
33/M	1.1	2.0 at Visit 9	Treated with IV tobramycin just prior to Visit 9. Final creatinine 1.2 at Visit 11.
12/M	0.7	1.1 at Visit 7	Concurrent AE of rhinitis noted. Final creatinine was 1.0 at Visit 11.
16/M	0.8	1.3 at Visit 8	Concurrent AE of rhinitis noted. Final creatinine was 0.8 at Visit 11.

Medical Officer Comment:

1. A review of the TOBI patients with ≥ 50% rises from their baseline serum creatinine reveal the majority of cases had just met this criterion, and resolution of the laboratory abnormality was noted by the final visit. TOBI does not appear to lead to any increased incidence of renal insufficiency compared to placebo, and the cases of elevated creatinine which occurred in the TOBI arm were mild and transient in nature.

Liver Function:

No trend in mean change from baseline for ALT, AST, and total bilirubin was noted in the parallel group studies. There were only two patients (one TOBI and one placebo) who had markedly abnormal ALT or AST values. The TOBI patient was an 11 year old male with AST value of 553 U/L which resolved to 42 U/L at the next visit. This abnormality was felt to be due to dehydration. In conclusion, therefore, TOBI did not appear to be associated with significant hepatotoxicity based on laboratory monitoring.

Electrolytes:

There were 12 patients (3 TOBI and 9 placebo) who had markedly abnormal electrolyte values during the parallel group studies. The 3 TOBI patients included a 32 year old female with a CO_2 value of 14.0 mmoles/L which was an isolated event that resolved at the next visit, a 15 year old male with two serum CO_2 value of 14.5 and 14.9 mmoles/L which was associated with worsening pulmonary symptoms, and a 17 year old female with an elevated serum potassium level of 10.5 mEq/L which was a hemolyzed sample. Therefore, TOBI did not appear to be associated with any clinically significant markedly abnormal laboratory values in these 3 patients.

WBC, Hemoglobin, Platelets:

There was no significant abnormalities regarding WBC and hemoglobin in the parallel group studies. Patients in both arms exhibited slight reductions in mean hemoglobin during the study, but these reductions never exceeded approximately 0.5 g/dL. Five TOBI and 3 placebo patients experienced markedly abnormal platelet values in the parallel studies. The 5 TOBI patients included one patient whose platelet count of 29,000 was attributed to lab error and one patient with platelet counts as low as 11,000 which were attributed to pseudothrombocytopenia (platelet clumping was noted, and platelets obtained in sodium citrate tubes and analyzed at an outside lab were within normal range). The remaining 3 TOBI patients with platelet abnormalities included one patient with ITP (platelet count of 45,000), one patient with end-stage liver disease (platelet count of 47,000), and one patient with markedly elevated platelets of 926,000 felt secondary to concurrent illness and coded as "unrelated to study drug." TOBI does not appear to be causally associated to serious changes in WBC, hemoglobin or platelet counts therefore.

III.N. The Emergence of Resistant Infections

III.N.(1). Background

Patients treated with TOBI received the drug in an intermittent fashion, with each cycle including

a 28 day on-drug period followed by a 28 day off-drug period. This regimen was selected, in part, to try to prevent the emergence of resistant microbiologic respiratory isolates.

The emergence of tobramycin resistance in respiratory isolates from cystic fibrosis patients is of great concern since aminoglycoside antibiotics are often one of the primary class of agents chosen to treat pulmonary exacerbations. To illustrate this, FDA analyzed the serious adverse events which required hospitalization during the parallel studies. In the TOBI arm, there were 130 events in 96 patients which required hospitalization. Of these 130 events, 106 (81.5%) required treatment with an intravenous aminoglycoside antibiotic with tobramycin being by far the predominant choice. In the placebo arm, there were 199 events in 120 patients. Of these 199 events, 162 (81.4%) required treatment with an intravenous aminoglycoside antibiotic which was almost always tobramycin.

Medical Officer Comment:
1. It is apparent from the review of serious adverse events which required hospitalization that aminoglycoside antibiotics, and particularly tobramycin, are frequently chosen as initial intravenous therapy. Emergence of organisms which are resistant to the aminoglycosides is therefore a critical safety concern.

III.N. (2). Sponsor's Database for Evaluating MIC Values
The sponsor performed multiple analyses to describe the emergence of *Pseudomonas aeruginosa* which were resistant to tobramycin. All analyses were performed on the ITT population. Of the two datasets of MIC values represented in the patient data listings (original and repeat), only values from the repeat dataset were used in the sponsor's analyses.

During a routine audit of the MIC laboratory at Children's Hospital in November of 1995, it was determined that there was inadequate documentation of quality control. On July 13 of 1996, additional problems with quality control and standard protocol were identified (QC strains were not run at the recommended frequency, QC trays contained inadequate tobramycin concentrations, and media used for inoculation of the trays with cation were adjusted). Following July 13, 1996, all MIC calculations were performed with good quality control, however.

As a consequence, the sponsor followed FDA recommendations that isolates obtained from patients prior to July 13 of 1996 at visits 3, 10, 11, and 16 be subcultured from frozen stocks and re-tested for MICs. The MICs derived initially were referred to as the "original" dataset, and the re-tests of the isolates were referred to as the "repeat" dataset. Original susceptibility results of isolates obtained and tested after July 13 of 1996 were therefore grouped with "repeat" MIC data to form the sponsor's MIC database.

In addition, the sponsor excluded specimens from all microbiologic analyses if they were collected less than 4 hours after the administration of study drug since this was a protocol deviation, or if this time difference could not be calculated. Specimens received in the lab more

than 2 days after the date of collection were also omitted. The following number of specimens were excluded by the sponsor at each visit:

Visit 3:	13 (2.5%)
Visit 10:	27 (6.0%)
Visit 11:	7 (1.5%)
Visit 16:	12 (28%)

III.N.(3). Sponsor's Analyses of MIC Values for *P. aeruginosa* Isolates

The following Table describes the frequency distribution of tobramycin MIC values at Visits 3, 10, 11 as provided by the sponsor. Each patient's highest MIC isolate at each visit was chosen for representation.

Sponsor's Analysis: Distribution of Tobramycin MIC Values at Visits 3, 10 and 11
(Highest MIC *P. aeruginosa* isolated for each patient at each visit)

	TOBI			Placebo		
MIC (ug/mL)	Visit 3 (n=254)	Visit 10 (n=224)	Visit 11 (n=224)	Visit 3 (n=254)	Visit 10 (n=226)	Visit 11 (n=223)
≤ 1	39.4%	30.8%	31.7%	48.8%	41.1%	49.3%
2 to 4	35.8%	33.9%	36.2%	31.1%	35.0%	33.6%
≥8*	24.8%	35.3%	32.1%	20.1%	23.9%	17.1%

*Comparing TOBI to placebo: Visit 3 p-value = .24; Visit 10 p-value = .01; Visit 11 p-value = < .001

Medical Officer Comments:

1. This analysis reveals that baseline MIC values tended to be somewhat higher in the TOBI arm compared to placebo. Additional analyses which compare each patients change from baseline MIC are therefore important since they control for this baseline imbalance. These will be explored in the FDA analyses of changes in MIC.

2. There is a statistically significant difference between TOBI and placebo arms of the relative percentage of patients who had MIC values ≥ 8 ug/mL at Visit 10 and Visit 11. This difference was not present at baseline. This finding is particularly notable in view of the fact that placebo patients, in general, spent more days on antipseudomonal antibiotics during the study. This suggests that inhaled tobramycin itself may cause a shift towards higher MIC values over time.

3. It does not appear that resistance patterns in the TOBI arm revert to baseline from the end of the third on-drug period (visit 10) to the end of the third off-drug period (visit 11). Thus, the "on drug-off drug" regimen for TOBI may not prevent the emergence of more resistant P. aeruginosa isolates.

In addition the sponsor examined changes in susceptibility by assessing the shifts in MIC values from baseline during the study for each patient using the *P. aeruginosa* isolate with the highest MIC. These results are shown below:

Sponsor's Analysis: Shifts in MIC from Baseline to Visits 10 and 11
(Highest MIC *P. aeruginosa* isolated at each visit)

	Visit 3 to Visit 10			Visit 3 to Visit 11		
	TOBI (n=222)	Placebo (n=220)	p-value TOBI vs placebo	TOBI (n=223)	Placebo (n=218)	p-value TOBI vs placebo
MIC increased[1]	15.8%	9.1%	.04	14.8%	2.8%	<.001
MIC unchanged[2]	80.2%	86.8%	NS	81.2%	91.3%	NS
MIC decreased[3]	4.1%	4.1%	NS	4.0%	6.0%	NS

[1]Patients with ≥ 4 fold increase in MIC between baseline and Visit 10 or 11
[2]Patients with MIC values +/- a 2 fold change between baseline and Visit 10 or 11
[3]Patients with a ≥ 4 fold decrease in MIC between baseline and Visit 10 or 11

Medical Officer Comments:

1. The large majority of patients in both arms had no significant change or a decrease in MIC during the study. Differences between TOBI and placebo arms for these categories were not significant.

2. A statistically significant greater percentage of TOBI patients experienced at least a 4-fold or greater increase in MIC values from baseline to Visit 10 and from baseline to Visit 11. These findings support the concern that TOBI therapy may be causing an upward shift in MIC values over time.

3. Resistance patterns in the TOBI arm do not appear to change from the end of the third on-drug period (visit 10) to the end of the third off-drug period (visit 11). Again, the "on drug-off drug" regimen for TOBI may not prevent the emergence of more resistant P. aeruginosa strains.

To help define whether the isolates with the highest MICs became the most prevalent population of organisms over time, the sponsor analyzed the frequency distribution of Tobramycin MIC values at Visits 3, 10, and 11 for all *P. aeruginosa* isolates, for highest MIC *P. aeruginosa* isolates, and for highest density *P. aeruginosa* isolates. The sponsor concluded that the tobramycin MIC values for the highest density *P. aeruginosa* isolates correlated most closely with the distribution of all *P. aeruginosa* isolates, rather than the distribution of the highest MIC isolates. Thus, it did not appear that the isolates with the highest MICs had become the most prevalent population within each group.

Medical Officer Comment:

1. The sponsor's conclusion that more resistant strains did not become the most prevalent population is true in this 6 month trial. Longer followup, however, is necessary to fully evaluate whether or not this would truly occur with chronic therapy.

Finally, the sponsor also analyzed the number and proportion of patients with isolates of *P. aeruginosa* with MIC values > 8 ug/mL (the traditional cutoff value for resistance) as shown below:

Sponsor Analysis
Percentage of Patients with Isolates of *P. aeruginosa* with Tobramycin MIC Values > 8 ug/mL

	TOBI (n=254 at Visit 3 and 224 at Visits 10 & 11	Placebo (n=254 at Visit 3, 225 at Visit 10, and 223 at Visit 11)	Diffence Between TOBI and Placebo
Visit 3	13.4%	10.2%	3.2%
Visit 10	25.9%	17.3%	8.6%
Visit 11	23.2%	8.1%	15.1%

Medical Officer Comments:
1. Slightly more patients in the TOBI arm (13.4% vs 10.2% placebo) had baseline P. aeruginosa isolates with MIC values > 8 ug/mL, although this difference was not statisitically significant. The relative percentage of TOBI patients with P. aeruginosa isolates having an MIC value > 8 ug/mL at Visits 10 and 11, however, were significantly greater than that noted in the placebo arm.

2. In summary, the sponsor's multiple analyses reveal a consistent finding of higher MICs over time in the TOBI arm compared to placebo. This occurred despite the fact that the TOBI patients spent less time on antipseudomonal antibiotics and had fewer hospitalizations compared to placebo patients. It therefore is reasonable to conclude that TOBI therapy itself is responsible for these upward shifts in the MIC values of Pseudomonas aeruginosa.

III.N.(4) FDA Database for Evaluating MIC Values
FDA reviewed MIC data for *P. aeruginosa* obtained in all patients as provided in Table 12.2.7 of the NDA submission. Only laboratory data using adequate quality control (i.e. repeat MIC values or original MIC values obtained after July 13, 1996) were considered in the FDA analyses. Unlike the sponsor, FDA did not exclude MIC values from the small number of specimens collected outside of protocol standards. While these specimens may have had inaccurate culture data or CFU counts, the MIC data obtained was felt to be valid. The maximum MIC for *Pseudomonas aeruginosa* isolates at Visit 3, Visit 10, and Visit 11 were recorded for each patient. In addition, each patient's maximum MIC at their last visit was recorded.

There were 220 placebo and 218 TOBI patients who had Visit 3, 10 and 11 MIC data for *Pseudomonas aerugniosa* isolates. Shifts in MIC from Visit 3 to Visit 10, and from Visit 3 to Visit 11 were evaluated in this group of patients. In addition, there were 246 placebo and 250 TOBI patients who had Visit 3 and a last visit MIC value where the last visit was visit 5 or beyone (i.e. patient had completed at least one cycle of study drug therapy). Shifts in MIC from Visit 3 to the last visit were evaluated in this group of patients.

III.N.(5) FDA Analyses of MIC Values for *P. aeruginosa* Isolates

Since there was a minor imbalance in baseline MIC values for *Pseudomonas aeruginosa* isolates (i.e. MIC values were slightly lower at baseline in the placebo arm), the primary FDA analyses focused on changes in MIC from baseline. The relative percentage of patients within each study arm who at least $\geq$ 4 fold rises and $\geq$ 8 fold rises in MIC from Visit 3 to Visit 10 and Visit 3 to Visit 11 were calculated. Results of these analyses follow:

FDA Analysis:
Fcld Changes in MIC from Visit 3 to Visit 10 and Visit 3 to Visit 11
(Highest MIC for *P. aeruginosa* isolated at each visit)

	Visit 3 to Visit 10			Visit 3 to Visit 11		
Fold Change in MIC	TOBI (n=218)	Placebo (n=220)	p-value	TOBI (n=218)	Placebo (n=220)	p-value
$\geq$ 4 fold rise or more	33.5%	20.0%	.001	26.1%	14.5%	.002
$\geq$ 8 fold rise or more	22.0%	10.0%	<.001	17.0%	4.1%	<.001

Medical Officer Comments:

1. This analysis demonstrates that a significantly greater percentage of TOBI patients had rises in MIC from baseline comparing Visit 3 to Visit 10, and Visit 3 to Visit 11. This was consistent for those with at least a 4-fold as well as at least an 8-fold rise in MIC.

2. The percentage of patients with 4-fold and 8-fold rises in MIC noted in both the placebo and TOBI arms decreased from Visit 10 to Visit 11. The magnitude of this decrease in both arms was approximately 6-7%. This suggests that there is some normal fluctuation in MIC values over time. Regardless of this variablility, the TOBI arm consistently had a significantly greater percentage of patients with rises in MIC when compared to the placebo arm.

FDA also examined changes in susceptibility by assessing the shifts in MIC values from baseline to the final study visit for 246 placebo and 250 TOBI patients. The last visit with valid MIC data was Visit 11 for approximately 80% of both TOBI and placebo patients. The remaining data

came from either Visit 10 (4-5% in both arms), before visit 10 (4-5% in both arms) or after Visit 11 during the open-label trials (10-11% in both arms). Results of this analysis follow:

FDA Analysis:
Fold Changes in MIC from Visit 3 to Last Study Visit
(Highest MIC for *P. aeruginosa* isolated at each visit)

Fold Change in MIC	Visit 3 to Last Study Visit		
	TOBI (n=250)	Placebo (n=246)	p-value
≥ 4-fold rise or more	28.8	16.8%	.001
≥ 8-fold rise or more	17.5	6.9	<.001

Medical Officer Comment: *This analysis also demonstrates that a significantly greater percentage of TOBI patients had at least 4-fold and 8-fold rises in MIC from baseline to final MIC.*

In summary, these analyses consistently show that more TOBI than placebo patients had 4-fold and 8-fold upward shifts in their MIC values from baseline to Visit 10, Visit 11, or the last study visit.

The FDA analyses of 4-fold and 8-fold shifts in MIC are important in that they are not affected by any baseline imbalance in MIC distribution between study arms. The 4-fold analyses, however, include patients who went from an MIC of .25 to 1 ug/mL (not alarming to most clinicians), as well as those patients who went from an MIC of 4 to 16 ug/mL (possibly more concerning). Thus, this analysis does not completely describe what the actual changes in MIC were over time in each treatment arm.

To supplement the analyses of shifts from baseline MIC, the FDA also analyzed the relative percentage of patients in each arm who had MIC values > 8 ug/mL at Visits 3, 10, and 11. A cutoff of > 8 ug/mL was chosen since this is the traditional cutoff for tobramycin resistance when tobramycin is admnisitered intravenously. The results of this analysis follow:

FDA Analysis
Percentage of Patients with Isolates of *P. aeruginosa* with Tobramycin MIC Values > 8 *ug/mL*

	TOBI (n=218)	Placebo (n=220)	Difference Between TOBI and Placebo arms
Visit 3	14.2%	10.9%	+3.3%
Visit 10	26.6%	16.8%	+9.8%
Visit 11	22.9%	7.7%	+15.2%

Medical Officer Comments:
1. There is a baseline imbalance in MIC values > 8 ug/mL which favors the placebo arm modestly. Therefore, the differences between the TOBI arm and placebo arm were calculated for each study visit and were compared. While an additional 3.3% of TOBI patients had high MICs at baseline, this difference widened to almost 10% at Visit 10 and to approximately 15% at Visit 11.

2. The changes in MIC values > 8 ug/mL over time in the placebo arm are also noteworthy. This reflects the normal variablility in MIC over time which may be attributed to variations in the assay itself, to variations in sputum production over time, or to other factors. Administration of systemic anti-pseudomonal antibiotics was allowed during the study, and therefore some of the changes in MIC in both treatment arms may reflect these therapies.

Administration of systemic antipseudomonal antibiotic therapies other than inhaled tobramycin may also have affected shifts in MIC values. Therefore, FDA performed subset analyses of those TOBI and placebo patients who did not receive systemic antipseudomonal antibiotic therapy during the study. This resulted in a database of 159 (61%) TOBI and 127 (48.5%) placebo patients who had at least a baseline MIC value and a maximum MIC value at either Visit 10 or 11. Visit 10 and 11 data were combined in for these analyses in an effort to maximize the available database. Results of these analyses, which were performed by FDA statisitician Tom Hammerstrom, follow:

FDA Subset Analysis of Patients Not Exposed to Antipseudomonal Antibiotics
Fold Change in MIC Values: Maximum MIC at Visit 3 to Maximum MIC at Visit 10 or 11

Fold change in MIC	TOBI (n=159)	Placebo (n=127)	p-value
≥ 4-fold increase	29.0%	18.5%	.03
≥ 8-fold increase	21.0%	5.9%	<.001

FDA Subset Analysis of Patients Not Exposed to Antipseudomonal Antibiotics
Percentage of Patients with MIC > 8 at Visit 10 or Visit 11

	TOBI (n=159)	Placebo (n=127)
% Patients with MIC > 8 ug/mL	26%	13%

Medical Officer Comments:

1. The subgroup analyses of patients who were not treated with anti-pseudomonal antibiotics at all during the 6 month study, reveal that a statistically significant greater percentage of TOBI patients had at least an 8-fold or greater increase in MIC from beginning compared to the maximum MIC at Visit 10 or 11. In addition, there was a trend for a greater percentage of TOBI patients versus placebo patients to have at least a 4-fold or greater increase in MIC over time.

2. A significantly greater percentage of TOBI than placebo patients had MIC values > 8 ug/mL at Visit 10 or 11 than placebo patients. Both of these subset analyses confirm that TOBI itself may be causing the upward shifts in MIC values over time.

III.N.(5). Changes in MIC over time for Antibiotics other than Tobramycin

The sponsor provided MIC values for antibiotics other than tobramycin at Visit 3 and Visit 10. These antibiotics included aztreonam, ceftazidime, chloramphenicol, ciprofloxacin, ticarcillin, trimethoprim sulfamethoxazole, amikacin and gentamycin. Dr. Tom Hammerstrom evaluated the MIC values for each antibiotic over time in the TOBI arm compared to the placebo arm in section 4.2.ii. of his statisitical review. In summary, the median MIC shifted upwards for all three aminoglycoside antibiotics: tobramycin, amikacin and gentamycin. This was not apparent for the remaining antibiotics, however.

Medical Officer Comment: *These findings support the previous findings that TOBI results in upward shifts in tobramycin MIC values over time, and result in concern that cross-resistance to the aminoglycosides as a class may be occurring over time as well.*

III.N.(6) The Clinical Relevance of Resistant *Pseudomonas aeruginosa* Isolates

The clinical outcome of patients who develop resistant *Pseudomonas aeruginosa* isolates is of interest, although it is difficult to determine this in a study of only 6 months duration. There was no evidence, for example, that TOBI patients did worse clinically. In fact, with respect to FEV-

1, the time to IV antibiotic use, and the time to first hospitalization, the TOBI patients did significantly better than the placebo patients. The efficacy reviewer for this NDA, Dr. John Alexander, explored various efficacy outcomes in patients with high MICs for *P. aeruginosa,* or with other resistant isolates at baseline. The reader is referred to his efficacy review for additional details. Briefly, however, Dr. Alexander found no evidence that having baseline resistant *Pseudomonas aeruginosa* isolates led to any poorer outcome with respect to FEV-1, time to IV antibiotics, or time to hospitalization. Patients with resistant *S. maltophilia* at baseline, however, did not tend to do as well regarding these efficacy endpoints. Thus the presence of resistant *S. maltophilia* at baseline may result in a less optimal response to inhaled tobramycin.

Few patients discontinued either the parallel studies. These patients, however, may help provide critical clues regarding important negative prognostic factors associated with premature study withdrawal. FDA therefore carefully evaluated the occurrence of resistant infections in all patients who withdrew from the parallel trials. Twenty-one placebo patients withdrew from the parallel trials. Of these, no patient was withdrawn for clinical concerns of resistance. Four patients, however, were noted to have *P. aeruginosa* isolates with MIC $\geq$ 8 ug/ml at their final study visit, and one of these four subjects also had *S. maltophilia* with an MIC of 256 ug/ml detected at the final study visit. In comparison, sixteen TOBI patients withdrew prematurely from the parallel trials. Of these, one withdrew due to a clinical concern of "resistant *Pseudomonas aeruginosa* pneumonia." Six additional subjects had *P. aeruginosa* isolates with MIC $\geq$ 8 ug/ml at their final study visit. An additional three patients had *S. maltophilia* with an MIC $\geq$ 32 ug/ml at their final study visit, and one additional patient had *A. xylosoxidans* with an MIC of 512 ug/ml at the final visit. In conclusion, therefore, there was evidence of resistant infections in 4 of 21(19%) placebo patients and in 11 of 16 (69%) of TOBI patients who withdrew prematurely from the parallel trials. This data suggests that the emergence of resistant infections may not only be more apparent in the laboratory, but that they may be clinically relevant as well.

FDA also reviewed the records of all 6 patients who were withdrawn from either the parallel or open-label trials due to the clinical concern of resistance. These records are summarized below:

Patient (TOBI/TOBI): (withdrew from study on day 139 during open-label)
PI stated: "Patient became resistant to tobramycin. This patient has developed multiple resistant strains of pseudomonas." The site provided the sponsor with culture results which stated "very light growth of pseudomonas aeruginosa; very resistant isolate." The same report sited "heavy growth of staphylococcus aureus; methicillin resistance." Interestingly, the testing of MICs by the sponsor reported all *P. aeruginosa* isolates having MICs $\leq$ 1 ug/mL during the study.

Patient (TOBI/TOBI): (withdrew from study on day 107 during open-label)
PI stated: "Patient needed concurrent aerosolized colistin due to pseudomonas being resistant to multiple antibiotics." Testing of MICs by the sponsor reported all MICs $\leq$ 2 ug/mL during the study, although *S. maltophilia* was present at all visits and was resistant to tobramycin.

Patient (TOBI): (withdrew from study on day 25 during parallel group study)
PI stated: "Following visit 6, patient was seen by her primary physician due to increases in other pulmonary symptoms.

Sputum results from Visit 5 showed a pseudomonas culture that was multiply resistant. Outside of antibiotic therapy, the bacteria was only sensitive to colistin." Testing of MICs by the sponsor reported a baseline *P. aeruginosa* Visit 3 MIC value of 8 ug/mL. All other MICs used in the sponsor's data analysis for *P. aeruginosa* were $\leq$ 4 ug/mL during the patient's study participation.

Patient _____ (TOBI/TOBI): (withdrew from study on day 110 during open-label)
PI stated: "Patient experienced pulmonary exacerbation while on cycle 4 of open-label that required hospitalization. Culture done at our lab grew out MRSA and *S. maltophilia.* Neither organism was susceptible to tobramycin. We felt that using inhaled gentamycin (MRSA is sensitive) was the best choice." Testing of MICs by the sponsor showed *P. aeruginosa* MIC values at Visits 3 and 10 of 8 ug/mL; *S. maltophilia* was also grown at Visits 11 and 13.

Patient _____ (Placebo/TOBI): (withdrew from study on day 83 after completing once cycle of open-label TOBI therapy)
PI stated: "Patient is withdrawing from the study at time of Visit 13. Patient is beginning colistin therapy in hopes of eradicating his pan resistance which is excluding him from possible lung transplantation." Testing of MICs by the sponsor reported *P. aeruginosa* at Visit 10 prior to TOBI dosing with an MIC of 8 ug/mL. *P. aeruginosa* strains at Visits 11 and 13 (before and after the first cycle of TOBI during open-label) had MICs $\leq$ 4 ug/mL.

Patient _____ (Placebo/TOBI): (withdrew from study on day 64 after one cycle of open-label TOBI)
PI stated: "Patient had resistant organisms and did not do well in first part of study. She responded well to IV colistin in hospital and wishes to continue aerosolized colistin." Testing of MICs by the sponsor reported *P. aeruginosa* at visits 3, 10, and 11 (all while on placebo) with MICs of 32, 16, and 32 ug/mL, respectively. The MIC of *P. aeruginosa* after one cycle of TOBI at Visit 12 increased to 64 ug/mL.

Medical Officer Comment:
1. Although only 6 patients withdrew from the study due to the clinician's concern of emerging resistant organisms, it is notable that all 6 were discontinued while receiving TOBI. No patients discontinued while receiving only placebo. This again supports the concern that clinically significant resistant infections may occur over time with TOBI therapy.

III.O. Superinfections in the Parallel Group Studies
Chronic antibiotic therapy may be associated with the development of superinfection with pathogens other than *Pseudomonas aeruginosa.* The sponsor and the FDA therefore analyzed cases of superinfection with other resistant gram negative organisms, and cases with gram positive and fungal pathogens.

III.O. (1). Superinfections with Resistant Gram Negative Organisms
Three tobramycin resistant gram negative pathogens were noted during the parallel group studies and are demonstrated in the following analysis by the sponsor:

Sponsor's Analysis
Treatment Emergent Resistant Gram Negative Infections at Visits 10 or 11 (whichever was the last visit)
Parallel Group Studies

Organism	TOBI (n=258)	Placebo (n=262)
B. cepacia	0	1
S. maltophilia	6	10
A. xylosoxidans	1	3

Medical Officer Comment:

1. The emergence of gram negative infections which were tobramycin resistant were balanced in the TOBI and placebo arms, and overall were uncommon in this analysis by the sponsor which focused on culture data obtained at the last visit (Visit 10 or 11) with evaluable microbiologic data. Unfortunately, the emergence of resistant gram negative infections during the overall study is unclear, since valid MIC data is only available at baseline and the end of the study.

FDA reviewed the available culture data and calculated the relative number of treatment emergent resistant gram negative infections at Visit 10 or 11 since valid MIC data was available at both of these visits, and this allowed a majority of TOBI and Placebo patients to be analyzed. The results of this analysis are shown below:

FDA Analysis
Treatment Emergent Resistant Gram Negative Infections at Visit 10 or 11
Parallel Group Studies

	TOBI (n=244)	Placebo (n=241)
B. cepacia	1	2
S. maltophilia	32	29
A. xylosoxidans	9	8
Flavobacterium sp	7	8
Nonfermenting GNR	9	2
Miscellaneous	2	1
Total # Infections	60	50
Total # Patients with Infections	55 (22.5% of pts)	49 (20.3% of pts)

*Miscellaneous for TOBI: *E cloacae* and *S marcescens*; Miscellaneous for placebo: *C freundii*

Medical Officer Comment:

1. FDA analysis of resistant gram negative infections at Visit 10 or 11 reveal a greater number of pathogens than the sponsor's analysis of the last available visit during the parallel trial. No

significant differences are noted, however, between treatment arms in either the sponsor's or the FDA's analyses. There does not appear to be any increased risk of resistant gram negative infections with the use of TOBI.

III.O.(2) Superinfections with Gram-Positive and Fungal Pathogens

Superinfections with gram-positive and fungal pathogens as provided by the sponsor are described below:

Treatment Emergent Gram-Positive and Fungal Infections at Baseline (Visit 3) and Visit 10
Parallel Group Studies

Organism	TOBI (n=258) Visit 3	Placebo (n=262) Visit 3	TOBI (n=234) Visit 10	Placebo (n=234) Visit 10
H. influenzae	11	12	0	7
S. aureus	109	91	78	93
S. pneumoniae	6	10	3	7
Aspergillus sp.	52	62	70	47
C. albicans	110	109	134	110
Other fungal pathogens	14	8	12	5

Medical Officer Comment:

1. There is no increased risk for gram-positive or fungal infections in the TOBI arm. Rates of C. albicans(approximately 40% in both arms) were much higher than the 6% prevalence reported in the Cystic Fibrosis Registry. This appears to represent colonization, however, since no patients were reported to have fungal pneumonia in this study.

IV. Safety Review of PC-TNDS-004: The Open-Label Study

A total of 68 patients from the parallel studies entered the open-label study: 33 had been on placebo and were receiving TOBI for the first time, and 35 were patients who had been on TOBI and elected to stay on it in the open-label trial.

IV.A. Adverse Events in the Open-Label Study

Adverse events during the open-label trial were similar to those noted during the parallel trials. Notably, the percentage of patients reporting voice alteration did not increase during the open-label studies, and no cases of tinnitus occurred during the open-label follow-on study. Thus, there did not appear to be any increased toxicities noted with longer exposure to TOBI.

IV.B. Patient Discontinuations from Open-Label Study

A total of 13 patients withdrew from the open-label follow-on study. Six of these patients had been on placebo during the randomized study, and withdrew from TOBI for the following reasons:

Placebo/TOBI Patients Who Withdrew from Open Label Trial

Patient ID	PI Reason for Study Withdrawal	Was MIC for *Pseudomonas aeruginosa* at final study visit > 8 ug/mL?	Were Other New Resistant Infections Noted?
	"Patient wanted to begin aerosolized colistin."	No	None.
	"Patient began aerosolized colistin in the hopes of eradicating pan-resistance to get on a lung transplant list."	No	None.
	"Patient had resistant organisms and did not do well on placebo; patient wanted to go on aerosolized colistin."	MIC at V3 was 32 ug/mL and went up to 64 ug/mL at V12.	None.
	"Patient had increased respiratory symptoms with first cycle of TOBI and opted not to continue."	MIC at V3 was 0.5 ug/mL and went up to 128 ug/mL at V16.	None.
	"Patient complained of throat and airway irritation."	No	None
	"Patient complained of headaches on TOBI."	No	None.

In summary, two patients withdrew due to clinical concerns of resistance. Of the remaining four patients, one patient had developed a highly resistant strain of *P. aeruginosa* by the end of the open-label trial and had withdrawn due to "increased respiratory symptoms." Thus, three of the six Placebo/TOBI subjects may have had resistant infections as a contributing cause for their decision to discontinue the open-label trial.

Seven patients had been on TOBI during the randomized study and withdrew during open-label for the following reasons:

TOBI/TOBI Patients Who Withdrew from Open Label Trial

Patient ID	PI Reason for Study Withdrawal	Was MIC for *Pseudomonas aeruginosa* at final study visit > 8 ug/mL?	Were Other Resistant Infections Noted?
	"Patient had organisms, including *P. aeruginosa*, which were multiply-resistant."	No	S. maltophilia noted at visits 7, 8, 10, and 11 with MIC ranging from 512 to 64
	"Patient needed aerosolized colistin due to resistant *S maltophilia.*"	No	S. maltophilia noted at baseline with MIC of 128 at V-3. It persisted thru visits 11-15 with higher MICs of 2048.
	Patient had pulmonary exacerbation with MRSA and resistant *S. maltophilia.* Physician decided to switch to aerosolized gentamycin.	No-valid MIC data for Visits 11 and 13 were not available so it was difficult to determine this.	S. maltophilia noted for the first time at visits 11 and 13 with MIC of 2048
	"Patient felt better on TOBI and wanted to receive it on a daily basis."	MIC at Visit 3 was 16 and rose to 64 at visit 13.	None
	"Patient felt no better on TOBI and is now on IV therapy."	MIC at Visit 3 was .25 and rose to 32 at Visit 11	None
	" Patient complained of bronchospasm, dyspnea and chest tightness during cycle 3."	No.	None
	Patient had no improvement on TOBI, and M.D. decided to switch to aerosolized colistin.	No	S. maltophilia noted for the first time at visits 5, 8, 10, and 13. Final MIC at V-13 was 2048.

In summary, three patients withdrew due to clinical concerns of resistance. Of the remaining four patients, two had developed *Pseudomonas aeruginosa* isolates having MICs above 8 ug/mL) and one had developed a new infection with *S. maltophilia* (018-005). Thus, six of the seven TOBI/TOBI subjects may have had resistant infections as a contributing cause for their decision to discontinue the open-label trial.

Medical Officer Comment:

1. Resistance, either to Pseudomonas aeruginosa or due to the emergence of other new infections, was fairly common in both the Placebo/TOBI and the TOBI/TOBI patients who withdrew from the open label trials. Again, this supports concern that the emergence of resistant organisms may have clinical relevance over time.

IV.C. *Pseudomonas aeruginosa* MIC Values in Patients Completing the Open-Label Trial
Twenty-eight of 35 TOBI and 27 of 36 placebo patients entered and completed the open-label study. Analyses of MIC values over time for *Pseudomonas aeruginosa* in these subjects is summarized below:

FDA Analysis of Patients Who Completed the Open Label Trial
Shifts from Baseline MIC to Final Available MIC for *Pseudomonas aeruginosa* Isolates

	Visit 3 to Final Visit in Open Label Trial		
	TOBI/TOBI (n=28)	Placebo/TOBI (n=27)	p-value TOBI/TOBI vs Placebo/TOBI
MIC increased[1]	17 of 28 (60.7%)	8 of 27 (29.6%)	.03
MIC unchanged[2]	10 of 28 (35.7%)	14 of 27 (51.9%)	NS
MIC decreased[3]	1 of 28 (3.6%)	2 of 27 (7.4%)	NS
MIC data not available at baseline	0	3 of 27 (11.1%)	NS

[1]Patients with ≥ 4 fold increase in MIC between baseline and Final Visit
[2]Patients with MIC values +/- a 2 fold change between baseline and Final Visit
[3]Patients with a ≥ 4 fold decrease in MIC between baseline and Final Visit

FDA Analysis of Patients Who Completed the Open Label Trial
Percentage of Patients with Isolates of *P. aeruginosa* with Tobramycin MIC Values > 8 ug/mL

	TOBI/TOBI (n=28)	Placebo/TOBI (n=27)
% At Visit 3	17.9%	7.4%
% at Last Visit	32.1%	11.1%
Change from Visit 3 to Last Visit (%)	+14.2%	+3.7%

Medical Officer Comment:
1. The above analyses demonstrate that MIC values increased over time in both TOBI/TOBI and Placebo/TOBI patients, but that increases were more dramatic in the TOBI/TOBI patients. These analyses support the concern that resistant Pseudomonas isolates may emerge with longer term TOBI treatment.

V. Summary of Safety

In summary, this safety review reveals that voice alteration and tinnitus were more common in the TOBI than in the placebo arms. In addition, upward shifts in MIC for *Pseudomonas aeruginosa* isolates were noted to be significantly greater in the TOBI versus placebo arm. Each of these safety findings is summarized briefly below:

Voice Alterations:

Voice alteration was clearly more common and more severe in TOBI patients. No patient suffered any permanent voice alteration, however, and the episodes were transient in nature. Voice alteration is known to also occur with inhaled DNA-ase therapy. The benefits of TOBI clearly support the use of this medication despite this particular adverse event.

Cochlear Toxicity:

The sole manifestation of cochlear toxicity in the studies which were reviewed was tinnitus. This adverse event occurred in 8 TOBI patients who had a total of 16 episodes versus no placebo patients. Tinnitus may be an early harbinger of aminoglycoside-induced ototoxicity, and is therefore very concerning. Again, the benefits of TOBI support its use, however ototoxicity should be carefully monitored by questioning patients for this particular adverse event. In addition, higher frequency audimetric evaluations may be helpful to determine the development of this complication with longer term use.

Changes in MIC for *Pseudomonas aeruginosa* isolates:

Frequency distribution summary curves of the fold changes in MIC from Visit 3 to Visit 10 and visit 3 to Visit 11 follow:

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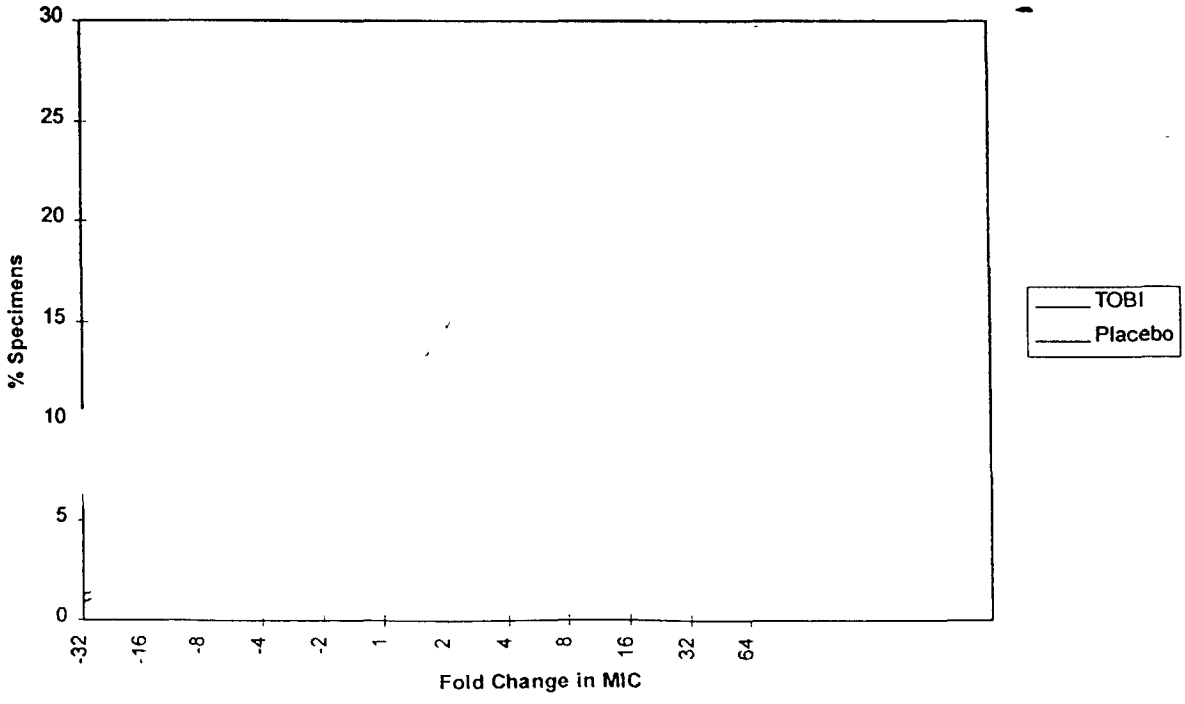
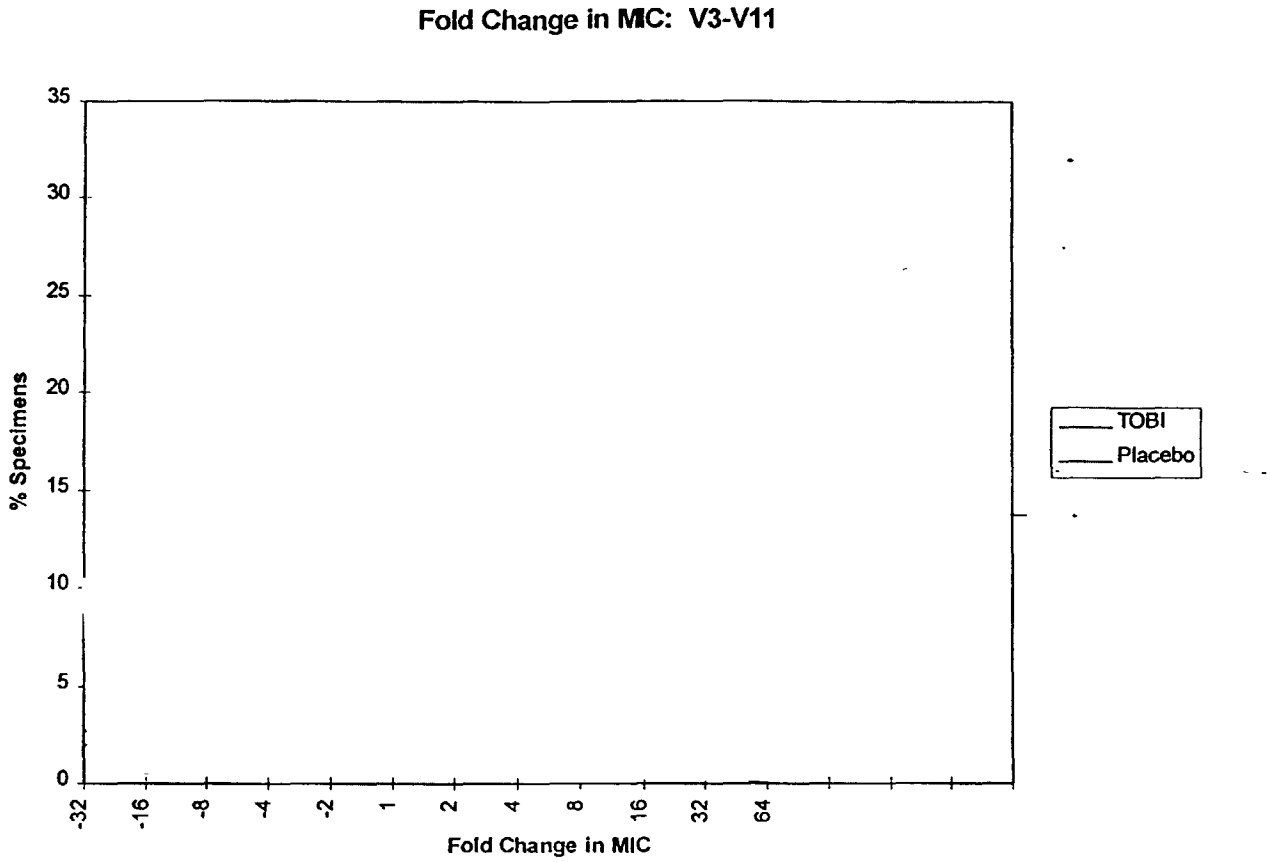
ON ORIGINAL

Fold Change in MIC: V3-V10





Each curve demonstrates that more TOBI patients had upward shifts in MIC over time. The clinical significance of these curves is unclear. There is no evidence in this 6 month trial that patients on inhaled tobramycin did worse than placebo patients; in fact, TOBI patients had greater improvements in FEV-1, spent fewer days on IV antibiotics, and spent fewer days in the hospital.

One potential explanation for the findings of continued clinical benefit despite the emergence of resistant organisms is that those resistant organisms, while more prevalent, may actually be less virulent. There were no virulence studies performed by the sponsor, however, to support this theory. An alternative explanation is that there simply has not been enough long-term followup to detect those patients who are failing due to resistant infections. Indeed, the FDA review suggests that subjects who withdrew prematurely often had resistant infections as a potential contributing factor. Therefore, the concern remains that longer term use of TOBI may eventually result in greater numbers of resistant *Pseudomonas aeruginosa* isolates, and that this may ultimately adversely affect clinical outcome.

/S/

concurrence:
HFD-520/Director/G. Chikami 8/4/98
HFD-520/Team Leader/J. Soreth 8/10/98

cc:
HFD-520/Medical Officer/J. Alexander
HFD-520/Chemistry/S. Pagay
HFD-520/Micro/J.King
HFD-520/CSO/B. Duvall-Miller
HFD-880/Biopharm/J.Zheng
HFD-725/Statistics/T. Hammerstrom
HFD-520/Pharmacology/A. Ellis
Original NDA 50-753
HFD-520/Div. Files

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-753

CHEMISTRY REVIEW(S)

HFD-520/ Duvall-Miller

OCT 3 1 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: #50-753 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 11-Sep-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	10-Jul-97	11-Jul-97	14-Jul-97
AMENDMENT/AC	21-Jul-97	24-Jul-97	28-Jul-97
Pre-Submission(NDA)	30-Apr-97	02-May-97	02-May-97
Pre-Submission (IND 46,945/Amendment)	21-Mar-97	24-Mar-97	24-Mar-97

NAME & ADDRESS OF APPLICANT: Pathogenesis Corp.
201 Elliott Ave. West
Seattle, WA 98119

DRUG PRODUCT NAME

Proprietary:	Tobi®
Nonproprietary/USAN:	Tobramycin Solution for Inhalation
Code Names/#'s:	MP-123456B
Chemical Type/ Therapeutic Class:	3-P

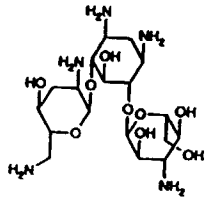
ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-infective

DOSAGE FORM:	Solution
STRENGTHS:	60 mg/ mL (5 mL ampule)
ROUTE OF ADMINISTRATION:	Inhalation
DISPENSED:	X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

O-3-Amino-deoxy-α-D-glucopyranosyl
-(1->4)-O-[2,6 diamino-2,3,6-
trideoxy-α-D-ribo-hexopyranosyl-
(1->6)]-2-deoxy-L-streptamine



$C_{18}H_{37}N_5O_9$

m.w. 467.52

CAS Registry No. 32986-56-4

Compendial Monograph: USP/NF volume 23, page 1558

SUPPORTING DOCUMENTS:

Tobramycin, AADA 63-345, Approved 11/30/93, DMF

Tobramycin, AADA 62-837, Approved 11/04/88,
Biogal Pharmaceutical Works, Ltd., Hungary

IND
IND
510 (K)

AMENDMENTS for IND

5/16/95: NDA Batches Stability Protocols.
9/8/95: Response to IND Chemistry Review 1 deficiencies & minor revisions in the manufacturing procedure and potency assay.
12/7/95:Response to IND Chemistry Review 1 deficiency comment 18.
4/18/96: Summary of the nine month stability data(Pre-NDA batches).
9/6/96 : Minor modification in the manufacturing procedure for the drug product solution.

RELATED DOCUMENTS (if applicable):

Chemistry Review 1 and Review 2 for IND

CONSULTS:

Facilities Inspection Requested Date 3/31/97- Pending
Request for Trademark Review Date 4/20/97. Status - The labeling committee approved the trade name
Methods Validation Request Date 7/28/97- Pending

REMARKS/COMMENTS:

Dr. Andrew Yu, reviewed the Methods Validation Package. Although, the method is similar to the USP monograph, method verification was requested to the Philadelphia District Laboratory.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 507 of the Act. Specific items which are not approvable are identified under the following headings: Drug Substance [Specifications and Analytical Methods, and Stability], Drug Product [Components and Composition, Specifications and Methods (drug product), Stability], Investigational Formulations, Methods Validation, and Establishment Inspections.

/S/

Shrikant N. Pagay, Ph.D. 10/31/97
Review Chemist

cc: Orig. NDA 50-753 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/Pagay/date
HFD-520/Alexander/
HFD-520/Ellis
HFD-520/Uratani
HFD-520/Duvall-Miller
HFD-520/Katague, DBK Init./Date-10/31/97
R/D Init by: SUPERVISOR
filename:N50-753

DEC 19 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: #50-753 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 19-Dec-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Pre-Submission (IND 46,945/Amendment)	21-Mar-97	24-Mar-97	24-Mar-97
Pre-Submission(NDA) CMC Document for initiating the review.	30-Apr-97	02-May-97	02-May-97
ORIGINAL	10-Jul-97	11-Jul-97	14-Jul-97
AMENDMENT/AC Label Information-Response to CMC comments	21-Jul-97	23-Jul-97	28-Jul-97
AMENDMENT/BC Additional specification (free of foreign matter) for drug substance.	24-Oct-97	27-Oct-97	31-Oct-97
AMENDMENT/BC Partial response to comments from CMC Review	25-Nov-97	26-Nov-97	2-Dec-97
AMENDMENT/BC Complete Response to comments from Review 1.	2-Dec-97 (Desk Copy)		

NAME & ADDRESS OF APPLICANT: Pathogenesis Corp.
201 Elliott Ave. West
Seattle, WA 98119

DRUG PRODUCT NAME

Proprietary:	Tobi®
Nonproprietary/USAN:	Tobramycin Solution for Inhalation
Code Names/#'s:	MP-123456B
Chemical Type/ Therapeutic Class:	3-P

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Anti-infective

DOSAGE FORM:	Solution
STRENGTHS:	60 mg/ mL (5 mL ampule)
ROUTE OF ADMINISTRATION:	Inhalation
DISPENSED:	X **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

O-3-Amino-deoxy-α-D-glucopyranosyl
-(1->4)-O-[2,6 diamino-2,3,6-
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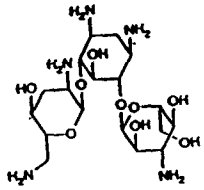
(1->6)]-2-deoxy-L-streptamine



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CAS Registry No. 32986-56-4

Compendial Monograph: USP/NF volume 23, page 1558

SUPPORTING DOCUMENTS:

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Biogal Pharmaceutical Works, Ltd., Hungary

IND
IND
510 (K)

AMENDMENTS for IND

5/16/95: NDA Batches Stability Protocols.
9/8/95: Response to IND Chemistry Review 1 deficiencies & minor revisions in the manufacturing procedure and potency assay.
12/7/95:Response to IND Chemistry Review 1 deficiency comment 18.
4/18/96: Summary of the nine month stability data(Pre-NDA batches).
9/6/96 : Minor modification in the manufacturing procedure for the drug product solution.

RELATED DOCUMENTS (if applicable):

Chemistry Review 1 and Review 2 for IND
Chemistry Review 1 for this NDA

CONSULTS:

Facilities Inspection: Acceptable 12/16/97 (see attachment)
Request for Trademark Review Date 4/20/97. Status - The labeling committee approved the trade name 6/23/97(see attachment)
Methods Validation Request Date 7/28/97- Completed(12/10/97)

REMARKS/COMMENTS:

This review (chemistry Review #2) includes responses from the firm for the Draft Comments which were based on the CMC Review#1. This review also includes for a quick reference the facility addresses for the drug substance and drug product manufacturing/testing/packaging and the drug product composition.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505(b) of the act. Specific items which are not approvable are identified under the following headings: Drug Substance [Specifications/ Analytical methods] and Drug Product:[Specifications and Methods, Container/closure, Stability].

/S/

12/19/97

Shrikant N. Pagay, Ph.D.,
Review Chemist

cc: Orig. NDA 50-753 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/Pagay/date
HFD-520/Alexander/Soreth/Mann
HFD-520/Ellis
HFD-520/Uratani
~~HFD-520/Duvall-Miller~~
HFD-520/Katague, Init./Date 12/19/97
R/D Init by: SUPERVISOR
filename:N50-753

Dunn Hill
520

DEC 22 1997

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: #50-753 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 21-Dec-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Pre-Submission (IND 46,945/Amendment)	21-Mar-97	24-Mar-97	24-Mar-97
Pre-Submission(NDA) CMC Document for initiating the review.	30-Apr-97	02-May-97	02-May-97
ORIGINAL	10-Jul-97	11-Jul-97	14-Jul-97
AMENDMENT/AC Label Information-Response to CMC comments	21-Jul-97	23-Jul-97	28-Jul-97
AMENDMENT/BC Additional specification (free of foreign matter) for drug substance.	24-Oct-97	27-Oct-97	31-Oct-97
AMENDMENT/BC Partial response to comments from CMC Review	25-Nov-97	26-Nov-97	2-Dec-97
AMENDMENT/BC Complete Response to comments from Review 1.	2-Dec-97 (Desk Copy)		
AMENDMENT Response to comments from CMC Review #2	17-Dec-97 (Fax Copy)		

NAME & ADDRESS OF APPLICANT: Pathogenesis Corp.
201 Elliott Ave. West
Seattle, WA 98119

DRUG PRODUCT NAME

Proprietary:	Tobi®
Nonproprietary/USAN:	Tobramycin Solution for Inhalation
Code Names/#'s:	MP-123456B
Chemical Type/ Therapeutic Class:	3-P

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-infective

DOSAGE FORM: Solution
STRENGTHS: 60 mg/ mL (5 mL ampule)

ROUTE OF ADMINISTRATION: Inhalation
DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

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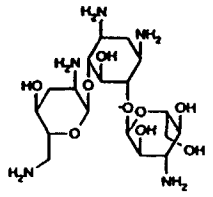
-(1->4)-O-[2,6 diamino-2,3,6-
trideoxy-α-D-ribo-hexopyranosyl-
(1->6)]-2-deoxy-L-streptamine



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Compendial Monograph: USP/NF volume 23, page 1558

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9/6/96 : Minor modification in the manufacturing procedure for the drug product solution.

RELATED DOCUMENTS (if applicable):

Chemistry Review 1 and Review 2 for IND
Chemistry Review 1, and Review 2 for this NDA

CONSULTS:

Facilities Inspection: Acceptable 12/16/97

Request for Trademark Review Date 4/20/97. Status - The labeling committee approved the trade name 6/23/97
Methods Validation Request Date 7/28/97- Completed(12/10/97)

REMARKS/COMMENTS:

This review (chemistry Review #3) includes drug substance and drug product Regulatory Specifications and post-approval commitments.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval for the chemistry, manufacturing and controls for this application under section 505(b) of the Act. The regulatory specifications and post-approval commitments for both the drug substance and the drug product are attached.

/S/

12/24/97

Shrikant N. Pagay, Ph.D.,
Review Chemist

cc: Orig. NDA 50-753 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/Pagay/date
HFD-520/Alexander/Soreth/Mann
HFD-520/Ellis
HFD-520/Uratani
HFD-520/Duvall-Miller
HFD-520/Katague, Init./Date 12/22/97
R/D Init by: SUPERVISOR
filename:N50-753