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Tobramycin Inhalation Powder NDA 201,688

FDA Anti-Infective Drugs Advisory Committee
September 5, 2012

John Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products, Office of New Drugs
Center for Drug Evaluation and Research, FDA

- Proposed Propietary Name: TOBI® Podhaler™
- The product may be referred to by the abbreviation “TIP” in the course of discussion today.

- Proposed Indication: Management of cystic fibrosis patients with *Pseudomonas aeruginosa*

- The product is a dry powder packaged in a hard capsule (strength 28 mg). Drug delivery is via a handheld, manually operated, breath activated dry powder inhaler (T-326).
- The active ingredient, tobramycin, is identical to the active ingredient in inhaled tobramycin solution (TOBI®) which is administered via nebulizer and was approved in 1997 for the same indication the applicant proposes for this product.

- Although dry powder inhalers are used in other areas, the product would be the first antibacterial dry powder delivered with a dry powder inhaler (DPI).
- Device considerations determine delivery (thus safety & efficacy) of the inhaled drug.
- Inhalers perform differently based on particle size and distribution patterns.
- Inhaler performance is influenced by human factors (usability and understanding of the Instructions for Use (IFU)).

Advisory Committee Discussion

- There are challenging review issues which would benefit from your advice and perspectives.
- Inhaled tobramycin solution (TOBI®) is a very important component of the care of most patients with cystic fibrosis as the majority eventually develop chronic *Pseudomonas aeruginosa* airway colonization.

Questions for the Committee

1. DISCUSSION: Please discuss the implications of the changes in minimum inhibitory concentrations (MICs) seen after treatment with tobramycin inhalation powder (TIP) compared to tobramycin solution for inhalation.

Questions for the Committee

2. VOTE: Has the applicant demonstrated adequate evidence of safety and efficacy to support the use of tobramycin inhalation powder (TIP) in the management of cystic fibrosis patients infected with *Pseudomonas aeruginosa*?
   - If you voted "Yes" in question 2, please discuss any recommendations concerning labeling of the product.
   - If you voted "No" in question 2, please discuss what additional data are needed.

Quantity of Evidence to Support Effectiveness

- In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval for a new drug, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well controlled investigations ("substantial evidence").

- In the Food and Drug Administration Modernization Act of 1997, Congress made it clear that the FDA may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute "substantial evidence" if FDA determines that such data and evidence are sufficient to establish effectiveness.
- Examples:
  - Different doses, regimens, or dosage forms of an approved drug
  - Single study with very convincing statistical results and internal consistency with supportive evidence

Medical Review Perspective- Trial Design, Safety and Useability

Shrimant Mishra M.D., M.P.H.
Medical Officer, DAIP

Anti-Infective Drugs Advisory Committee Meeting
Sept. 5th, 2012

Overview

- Broad discussion of tobramycin inhalation powder (TIP) drug development program
  - Phase 1 and Phase 3 trial designs
- Overview of safety results with focus on key findings
  - Increased use of antipseudomonals
  - Increased discontinuations
- Human factors study
  - Gaps in study design
  - Areas of concern

TIP Development Program

- Two Phase 1 Studies
  - Study TBM100INH007
  - Study TBM100CTPI001
- Three Phase 3 Studies
  - C2301
  - C2302
  - C2303

TIP Development Program

- Two Phase 1 studies
  - Study TBM100INH007
    - Open label, five period, crossover study to compare intrasubject/intersubject variability in pulmonary deposition and pharmacokinetics after inhalation of tobramycin dry powder and TOBI
    - Part A: 3 separate single radiolabeled doses of TIP to assess lung deposition/intrasubject variability of deposition by gamma scintigraphy.
    - Part B compared pharmacokinetics of typical TOBI dose and 6 inhalations of TIP
    - Single and multiple doses of dry powder capsule (25 mg capsule with 55% active tobramycin [13mg])
    - 14 Healthy volunteers; mean age 34 years; FEV1% Predicted > 80%

TIP Development Program

- Part A Conclusions: lung deposition was 34% with acceptable intra and intersubject variability (though there is clearly a broad range) and more deposition appeared to occur peripherally rather than centrally

- Part B Conclusions: TIP (6 capsules) and TOBI tobramycin serum concentrations rose at approximately the same rate, had similar half lives, and were absorbed into the serum from the lung at roughly equivalent rates. The TIP dose produced serum concentrations twice as high as the TOBI dose; dry powder had a four fold increase in lung delivery compared to nebulization

- Limitations: Older, healthy subjects with good pulmonary function (mean inspiratory flow rate 72 L/min.)

- Set stage for pursuing powder formulation and parameters for dose finding study

TIP Development Program

- Study TBM100CTPI001
  - Dose finding study
  - Single dose, dose escalation trial comparing safety and pharmacokinetics of several TIP doses and approved TOBI dose
  - 86 CF subjects ≥ 6 years old and FEV1 % predicted ≥ 40 %
  - Doses evaluated: Single doses
    - TIP cohorts –
      - a)28mg (2 x 14mg)
      - b)56mg (4 x 14mg)
      - c)56mg (2 x 28mg)
      - d)84mg (3 x 28mg)
      - e)112mg (4 x 28mg)
    - TOBI – 300mg/ 5 mL (nebulized solution)
  - Conclusions: 112 mg dose appeared to have serum PK parameters similar to that of TOBI 300mg/5ml though sputum PK parameters were more variable

TIP Development Program

- Study TBM100CTPI001
  - The administration of 112 (4x28) mg of TIP resulted in comparable serum and sputum exposures to 300 mg TOBI

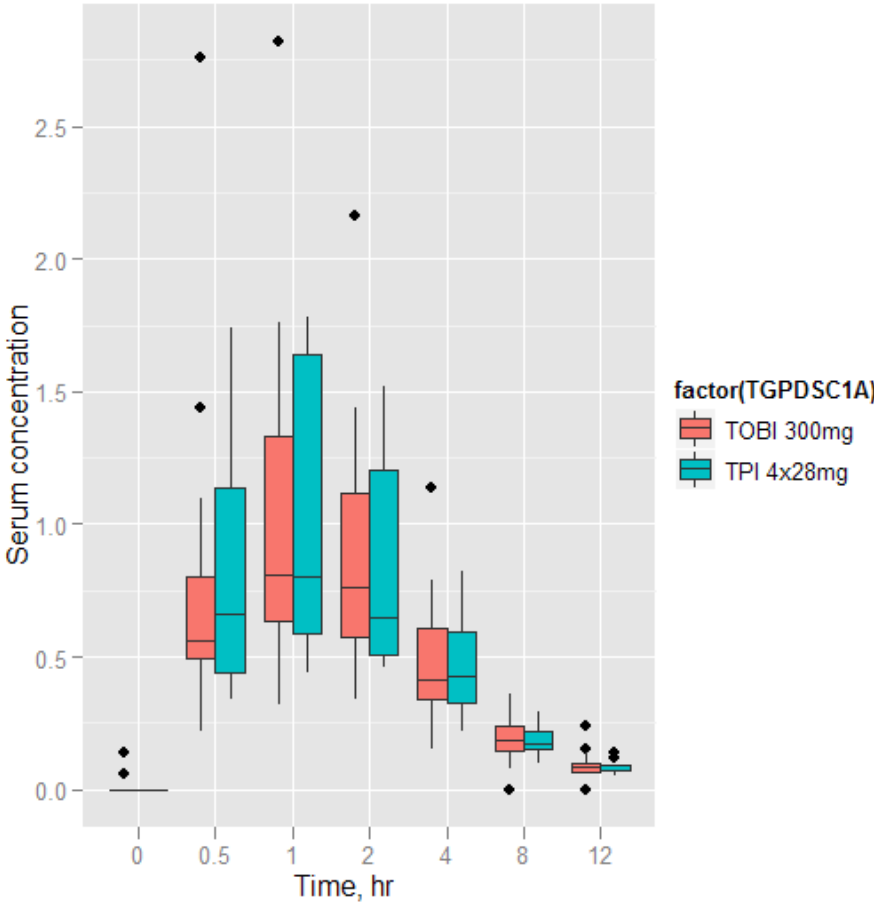
Treatment	Parameter	Serum (± SD)	Parameter	Sputum (±SD)
300 mg TOBI	C_{max} (µg/mL)	1.04 ± 0.58	C_{max} (µg/g)	737 ± 1028
	$AUC_{0-\infty}$ (µg*h/mL)	5.3 ± 2.6	$AUC_{0-\infty}$ (µg*h/g)	1302 ± 1127
112 mg TIP	C_{max} (µg/mL)	1.02 ± 0.53	C_{max} (µg/g)	1048 ± 1080
	$AUC_{0-\infty}$ (µg*h/mL)	5.1 ± 2.0	$AUC_{0-\infty}$ (µg*h/g)	1740 ± 809

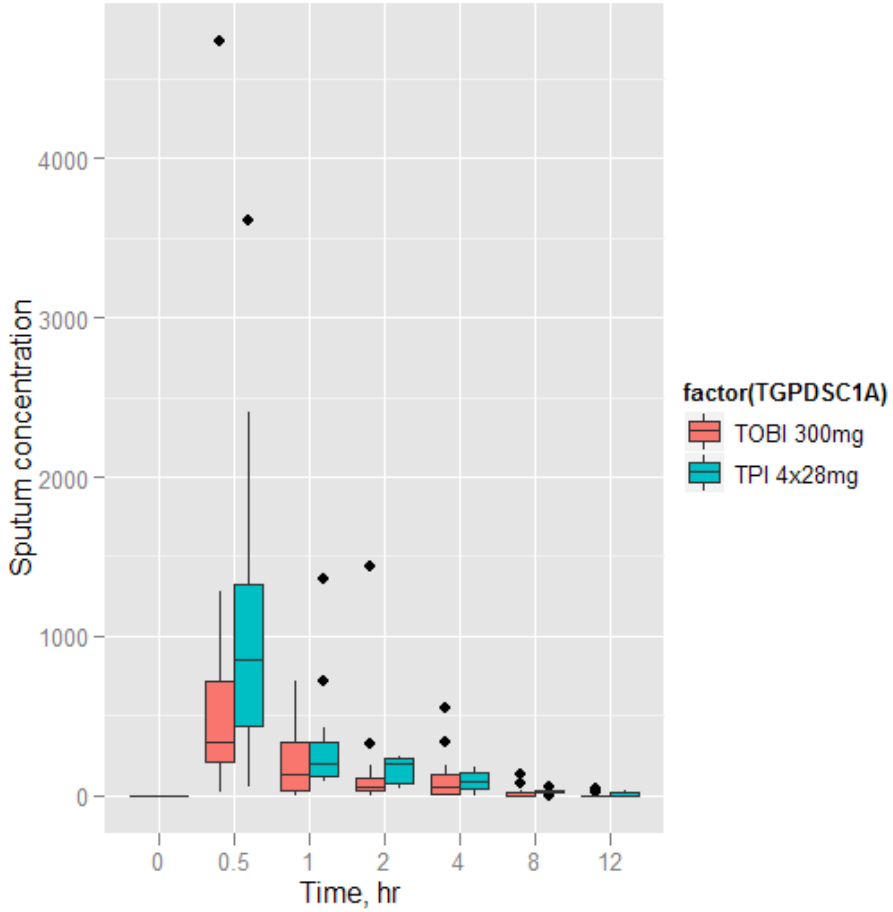
Adapted from Tables 11.4.1.1.1-1 and 11.4.1.1.3-1 from the TPI-001 Study Report

TIP Development Program

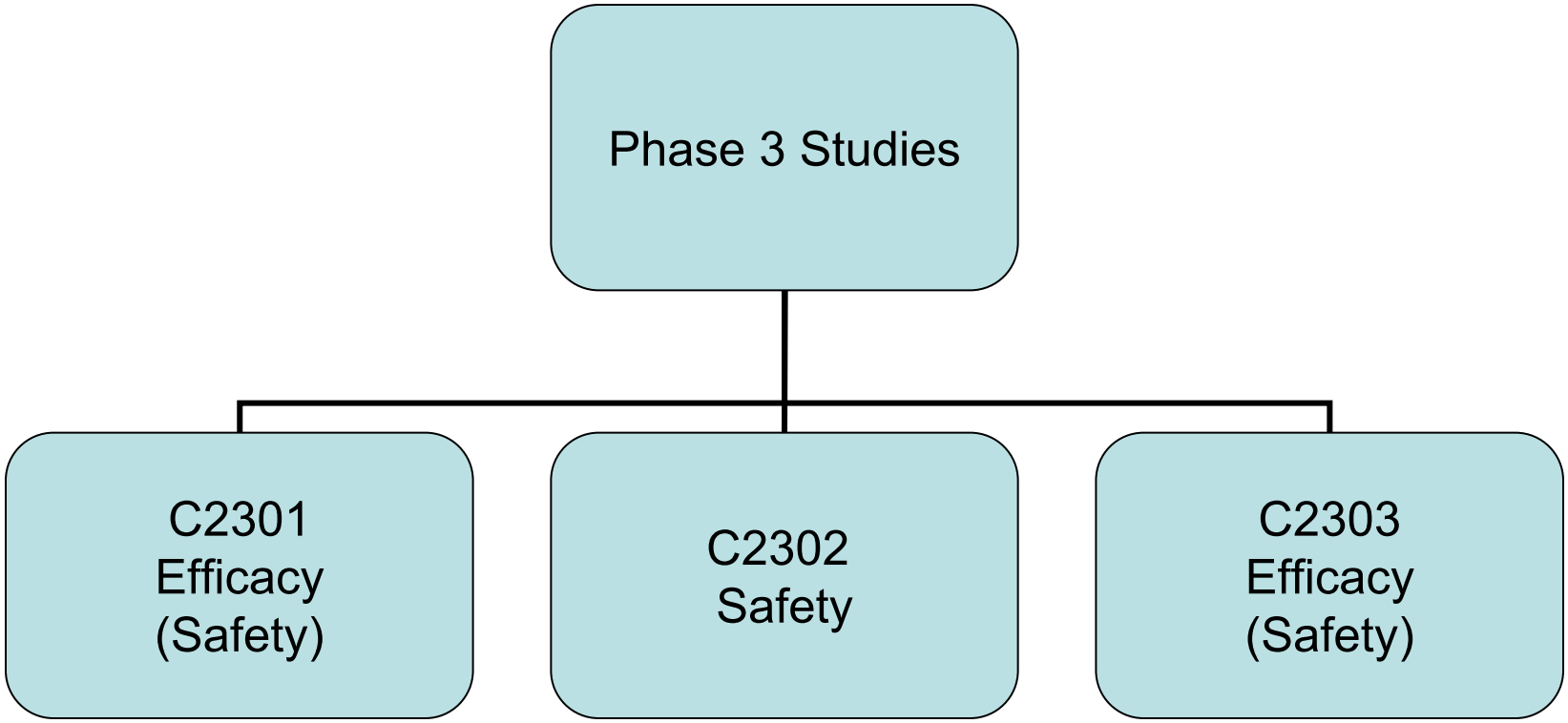
- Study TBM100CTPI001
  - The administration of 300 mg TOBI and 112 mg TIP resulted in comparable serum and sputum concentrations across the sampled time points

TIP Development Program: Study TBM100CTPI001





TIP Development Program



Dosing: 112 mg TIP twice a day (four 28 mg capsules twice a day)

Regimen: Cyclical CF paradigm for inhaled antipseudomonals (28 days on study drug followed by 28 days off study drug)

TIP Development Program

- C2301 and C2303
  - Efficacy related primary endpoint
  - Similar characteristics
    - Placebo controlled, blinded
    - Placebo was dry powder without active ingredient
    - Inclusion/Exclusion criteria similar
      - Age 6 to 21 years old; FEV1% predicted ≥ 25% and ≤ 80%
        - » Mean age 13 years old for both arms in both trials
      - No usage of inhaled antipseudomonals 4 months prior to study
    - Primary endpoint similar
      - Relative change in FEV1% predicted from Day 1 to Day 28
    - Small trials
      - C2301 safety population 95 subjects
      - C2303 safety population 62 subjects

TIP Development Program

- C2301 and C2303
  - Differences
    - Trial duration and design
      - C2301: Cycle 1 blinded and placebo controlled followed by 2 open label cycles where all subjects on TIP
      - C2303: Only one placebo controlled blinded cycle
    - Manufacturing Process
      - Process altered between studies C2302 and C2303
      - Formulation unchanged

Change in TIP Manufacturing Process

- A new manufacturing process for producing TIP was instituted prior to the conduct of C2303
- In addition to the clinical data from C2303, the sponsor performed multiple statistical analyses to compare the TIP serum PK from the new process to previous data
- These analyses support that the new manufacturing process used in C2303 did not significantly alter the serum pharmacokinetics of tobramycin

C2301 and C2303 Study Design

C2301	28 Days TIP or Placebo	28 Days Off	28 Days TIP	28 Days Off	28 Days TIP	28 Days Off
C2303	28 Days TIP or Placebo	28 Days Off	******	******	******	******

Blinded

Open Label

Cycle 1
Weeks 1-8

Cycle 2
Weeks 9-16

Cycle 3
Weeks 17-24

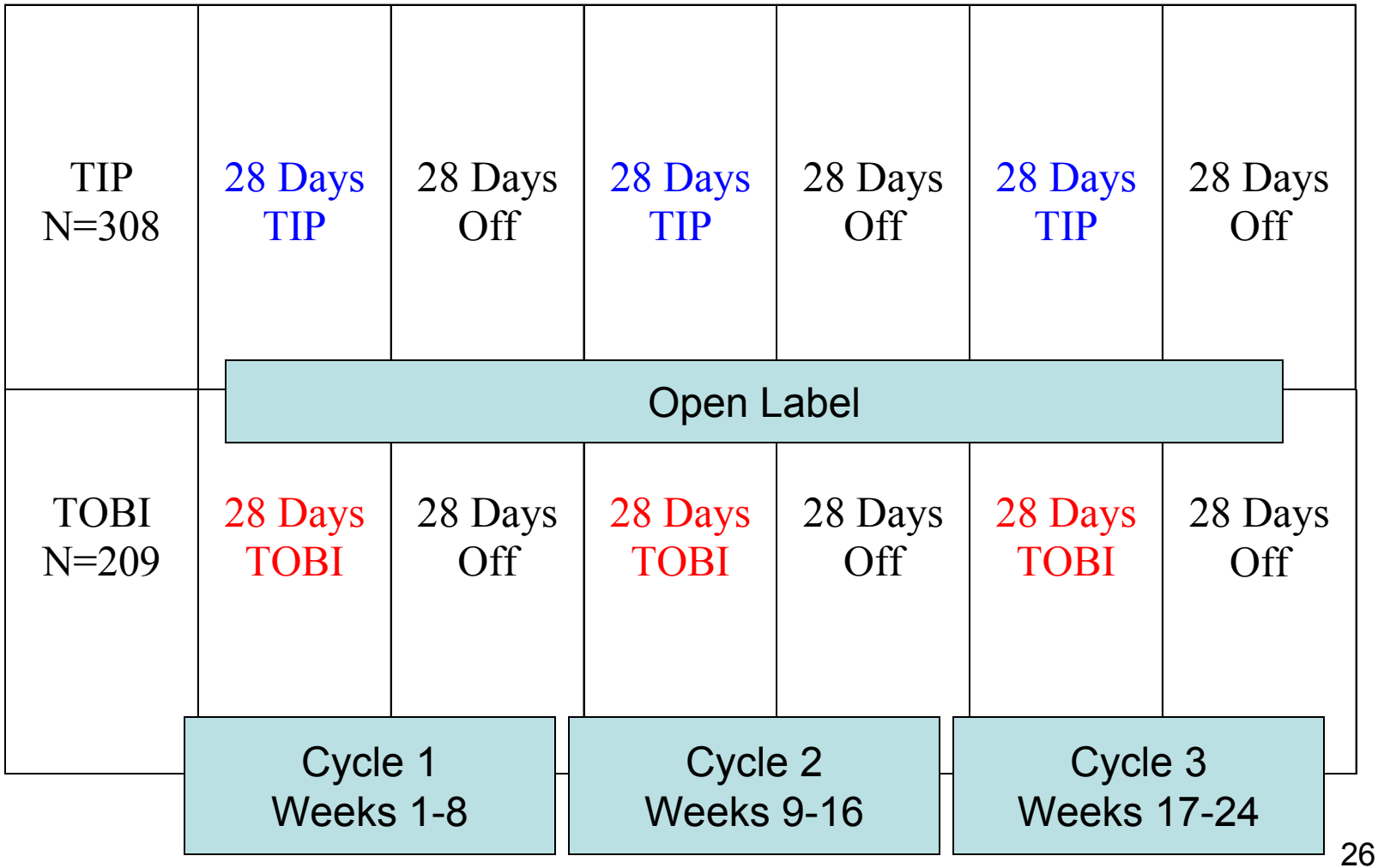
Safety Database

- Major Contributor
  - Study C2302
    - Main objective safety
    - 308 TIP subjects
- Minor Contributors
  - C2303, C2301
    - 76 TIP subjects combined
    - Comparator dry powder with excipients only
  - Phase 1 Studies
    - INH007: 14 healthy subjects
    - CTPI001: 86 CF subjects

C2302: Study Characteristics

- Open label, active controlled, multicenter study
- Three cycles of 28 days on drug/28 days off drug
- TOBI vs. TIP
  - TOBI®: 300mg/5ml nebulized solution twice a day
    - 209 subjects All Randomized Safety Population
  - TIP: 112mg inhaled powder twice a day
    - 308 subjects All Randomized Safety Population
- Inclusion/Exclusion Criteria
  - Allowed for subjects older than 20 years old
  - Allowed inhaled antipseudomonal experienced patients
    - Only off for 28 days prior to study

C2302: Study Design



C2302: Demographics

Subpopulation		TIP N=308	TOBI N=209
Age	≥ 6 and <13	28 (9%)	18 (9%)
	≥ 13 and< 20	66 (21%)	48 (23%)
	≥ 20	214 (70%)	143 (68%)
Sex	Male	171 (55%)	115 (55%)
	Female	137 (45%)	94 (45%)
Race	Caucasian	279 (91%)	189 (90%)
	Hispanic	20 (7%)	17 (8%)
Baseline FEV1 % Predicted[1]	< 25%	5 (2%)	10 (5%)
	≥25 to < 50%	117 (38%)	85 (41%)
	≥50 to ≤ 80%	173 (56%)	93 (44%)
	>80%	13 (4%)	21 (10%)

-Adapted from Clinical Study Report C2302

Safety: Deaths

- 3 deaths in C2302
  - All in TIP arm
  - Older CF patients (> 20 years old)
  - 2 cases reflect likely failure of TIP to prevent/lessen impact of pulmonary exacerbation
  - 1 case result of recreational drug use
- No TIP deaths in any other studies

Deaths: Case Study

- 21 year old male with a history of chronic sinusitis, cholecystectomy, and inhaled tobramycin use
- At baseline had heavy sputum *Pseudomonas aeruginosa* load (5.2 x 10^8 CFU/ml) and baseline FEV1% predicted of 39%
- During the 2nd off cycle, the subject had clinical signs of a pulmonary exacerbation (increased dyspnea, cough, sputum production)
- Hospitalized for six days and treated with multiple antipseudomonals.
- Discharged but then readmitted again with similar symptoms four days later and again treated with multiple antipseudomonals (including meropenem and piperacillin-tazobactam), vancomycin, and mucolytics
- The subject continued to deteriorate and died two weeks later.

- Adapted from CSR 2302

Safety: Serious Adverse Events

Treatment Arm	Number of Subjects With SAE
TIP N=308	
All SAEs	**85 (27.4%)**
Lung Disorder	60 (19.5%)
TOBI N=209	
All SAEs	**61 (29.2%)**
Lung Disorder	39 (18.7%)

- Adapted from Clinical Study Report C2302

Safety: Hospitalizations and Antipseudomonal Usage

- C2302
  - No difference in safety related hospitalizations
    - 25% for both arms
  - Increase in TIP usage of antipseudomonals
    - TIP: 200 subjects (65%) with new usage
    - TOBI: 114 subjects (55%) with new usage
    - Driven by non-inhaled usage, particularly ciprofloxacin usage
    - Time to first use: TIP 89 days vs. 112 days for TOBI

Safety: Antipseudomonal Usage

C2302 – New Ciprofloxacin Usage, By Treatment Arm and Demographic Subgroup

Arm	New Usage	Sex		Age (y)			FEV1 (% predicted)	
		M	F	≥6 to <13	≥13 to <20	≥ 20	≥25 to <50	≥50 to ≤75
TIP	146 (47%)	75 (44%)	71 (52%)	9 (32%)	31 (47%)	106 (50%)	63 (49%)	83 (46%)
TOBI	74 (35%)	40 (35%)	34 (36%)	10 (56%)	16 (33%)	48 (34%)	32 (36%)	42 (35%)

-Percentages represent All Randomized Safety Population demographics

-Patient was assessed for this time point for the course of the study (6 months) or until discontinuation

Safety: Antipseudomonal Usage

- C2301
  - Mildly decreased usage in TIP arm vs. placebo (1st cycle only)
    - TIP: 6 subjects/46 (safety population)= 13%
    - Placebo: 9 subjects/49 (safety population)= 18%
  - Similar findings in C2303

Safety: Common Adverse Events

- Pulmonary exacerbation-related
  - FEV decreased, chest discomfort, pyrexia, dyspnea exertional
- Local irritation
  - Dysphonia, oropharyngeal pain, dysgeusia, throat irritation, cough
  - Likely to be considered related adverse events

Safety: Common Adverse Events

C2302- Related Adverse Events Occurring At a Rate ≥ 2% Higher Than TOBI

Related AEs	TIP N=308	TOBI N=209
Cough	78 (25%)	9 (4%)
Dysphonia	39 (13%)	7 (7%)
Dyspnea	17 (5%)	3 (1%)
Productive Cough	14 (4%)	2 (1%)
Oropharyngeal Pain	14 (4%)	2 (1%)

-Adapted from Clinical Study Report C2302

Safety: Cough

C2302- Cough (Possibly or Probably Related) As a Function of Demographic Subgroups and Treatment Arm

Arm	Sex		Age (y)			FEV1 (% predicted)	
	M	F	≥6 to <13	≥13 to <20	≥ 20	<50 %	≥50 %
TIP	38/171 **22%**	41/137 **30%**	11/28 **39%**	18/66 **27%**	50/214 **23%**	34/122 **28%**	45/186 **24%**
TOBI	3/115 **3%**	6/94 **6%**	0/18 **0%**	1/48 **2%**	8/143 **6%**	2/95 **2%**	7/114 **6%**

-PTs analyzed were 'cough,' 'productive cough,' 'upper airway cough syndrome' and 'post-tussive vomiting'
-Denominators represent demographic subgroups of All Randomized Safety Population

Safety: Discontinuations

C2302- Discontinuations by Treatment Arm and Demographic Subgroup

	TIP (N=308) 83 Discontinuations	**TOBI (N=209)** 38 Discontinuations
Sex		
Male	47/171=**27**%	17/115=**15**%
Female	36/137=**26%**	21/94=**22**%
Age		
≥6 to <13 years old	1/28=**4**%	3/18=**17**%
≥13 to < 20 years old	12/66=**18**%	8/48=**17**%
≥ 20 years old	70/214=**33**%	27/143=**19**%
Baseline pulmonary function		
< 50 %, FEV1 % predicted	47/122=**39**%	20/95=**21**%
≥ 50 %, FEV1 % predicted	36/186=**19**%	18/114=**16**%

-Denominators represent demographic subgroups of All Randomized Safety population

Safety: Bronchospasm

C2302

- 5 (1.6%) subjects in TIP vs. 1 (0.5%) subject in TOBI reported 'bronchospasm'
- 12 subjects (3.9%) TIP vs. 3 (1.4%) subjects TOBI if also include term 'wheezing' (related events only)
- Primarily in oldest age group
- No event serious
- No clear difference in measured airway reactivity
  - Limited by missing data and assessment at only one post-dose time point

Safety: Bronchospasm

C2302: Number of Subjects with a Relative Decline in FEV1 % Predicted of ≥ 10 % from Pre- to Post- Dose, by Treatment Group & Visit Day, All Randomized Safety Population

Treatment	%FEV_1 decline	Day 1 n (%)	Day 7 n (%)	Day 28 n (%)	Day 56 n (%)	Day 84 n (%)	Day 112 n (%)	Day140 n (%)
TIP N=308	≥10 to <20 %	33 **(11)**	12 **(4)**	14 **(5)**	21 **(7)**	19 **(6)**	28 **(9)**	17 **(6)**
	≥ 20%	3 **(1)**	3 **(1)**	3 **(1)**	3 **(1)**	2 **(0.6)**	4 **(1)**	1 **(0.3)**
TOBI N=209	≥10 to <20 %	23 **(11)**	10 **(5)**	8 **(4)**	14 **(7)**	8 **(4)**	11 **(5)**	12 **(6)**
	≥ 20%	1 **(0.5)**	1 **(0.5)**	1 **(0.5)**	3 **(1)**	2 **(1)**	2 **(1)**	3 **(1)**

- Shown as percent of All Randomized Safety Population

Safety: Ototoxicity

- C2302: No clear evidence of increased ototoxicity compared to TOBI
  - Audiometry performed on subset of 78 TIP subjects and 45 TOBI subjects at visits 2,5,8,10
    - High frequency testing limited (8 kHz)
    - No formal vestibulotoxicity testing
  - 5 TIP and 3 TOBI subjects found to have significant changes over time[1]

1- as outlined by American Academy of Audiology
http://www.audiology.org/resources/documentlibrary/Documents/OtoMonPositionGuideline.pdf

Safety: Nephrotoxicity

- C2302
  - no real difference in nephrotoxicity noted between TIP and TOBI
  - Only 2 subjects in TIP arm and 2 subjects in TOBI arm has post baseline serum creatinine values ≥ 1.5 mg/dl
  - Minor differences in number of subjects with 50% increase from baseline serum creatinine level
  - Limited by missing data

Compliance

- Measured through a combination of evaluation of patient dosing logs and returned capsules/inhalers at the end of an “on” cycle
- Dosing cycle 28 days, but patient given supplies for 30 days of dosing
  - Extra two days could be used in compliance calculation
- Two doses a day
  - TIP dose= 4 capsules
  - TOBI dose= 1 ampule
- Compliance = number of doses taken over 30 day period/56 doses
  - Could range from 0% to 107% (60 doses/56 doses)
  - Overall compliance was mean compliance from the 3 cycles

Compliance

- C2302
  - TIP overall mean compliance: 90%
  - TOBI overall mean compliance: 94%

Comparison of Low Compliance (<80% compliance) by Cycle and Treatment Arm

Rates of Low Compliance (< 80% Compliance) n/N (%)			
	1st Cycle	**2nd Cycle**	**3rd Cycle**
TIP	36/308 (**12**)	35/264 (**13**)	38/234 (**16**)
TOBI	14/209 (**7**)	17/181 (**9**)	14/172 (**8**)

- denominator based on the numbers of subjects available at the beginning of that cycle to calculate

-adapted from Clinical Study Report C2302

Device Usability

- Human Factors (HF) study conducted by the applicant to evaluate the ability of different subgroups to properly use TOBI PodHaler

Device Usability: Three Phase Human Factors Study

1. **First Use Assessment:** Participants interviewed and trained to use the device. Instructions For Use (IFU) also available, but not required to use.

2. **5-Day Home Use:** A portion of participants evaluated device in a five day home use study where morning and evening doses were simulated.

3. **Post 1 Week Assessment**: The same portion of participants returned to participate in a Post One Week Assessment study which included a final observed simulation of inhalation, interview, and debriefing.

Device Usability: Human Factors Study

First Use Assessment Phase (n=62)

- To deliver the intended dose the following five critical steps should be performed:
  1. Remove the capsules from the blister pack
  2. Pierce the capsules
  3. Inhale from 4 capsules
  4. Inhaling twice from each capsule to empty the powder completely
  5. After inhaling twice, remove and check capsule to determine if pierced and empty
     - Only empty capsules used in all study phases
- Overall failure rate was 53% (33/62), even though all participants were trained on the use of the product prior to commencing the study

Device Usability: Human Factors Study

First Use Assessment Phase (n=62)

Participants with one or more critical errors on first attempt

Age group (years)	Number of Participants Who Made ≥ 1 Error
6 to 8 (n=16)	11
9 to 12 (n=15)	10
13 to 17 (n=15)	4
Over 18 (n=16)	8
Total (n=62)	33

Device Usability: Human Factors Study

First Use Assessment Phase (n=62)

Types of critical errors on first attempt

Age group (years)	Failure to Remove Capsule From Blister Pack	Incomplete Piercing	Failure to Inhale From 4 Capsules*	Failure to Inhale Twice From Each Capsule	Failure to Check Capsule Post-inhalation	Total number of observed critical errors**
6 to 8	0	2	2	8	3	15
9 to 12	0	2	3	4	5	14
13 to 17	0	0	0	3	5	8
Over 18	0	0	1	2	7	10
Total	0	4	6	17	20	47

*Includes use error coded as not inhaling n=4, US11, US37, US53 US58

**Some participants made more than one error, so the number of errors exceeds the number of participants that failed to deliver the dose correctly

Device Usability: Human Factors Study

Home Use Study (n=34)

- No observation of dose delivery
- Success evaluated by return of capsules
- Failure rate: 65% of participants (22/34) returned unpierced and/or dented capsules
  - 1-4 unpierced capsules / subject that failed
  - 2 dented capsules / subject that failed

Device Usability: Human Factors Study
Post 7-day Assessment (n=34)

- Insufficient # of participants
- 55.8% (19/34) incorrect dosing procedure
- 13/19 participants who failed at one week also failed on 1st attempt
- 7 participants that previously failed on 1st attempt went on to be successful at one week

Age group (years)	Number of Participants Who Made ≥ 1 Error
6 to 8 (n=10)	5
9 to 12 (n=7)	3
13 to 17 (n=8)	5
Over 18 (n=9)	6
Total (n=34)	19

Device Usability: Observations

- High failure rate in all three phases of HF study (53%, 65% and 56%)
  - Errors in delivering dose likely to occur in actual use
  - Even in the Home Use and Post One Week Assessment which include insufficient #'s of participants
- Training patients prior to use did not ensure successful dose delivery

Device Usability: Observations

- Unclear if IFU could improve success
  - Only 37% of participants consulted IFU, none thoroughly
  - In actual use, IFU may likewise not be consulted
- Failure to deliver dose on first attempt may predict unsuccessful use
  - Most participants who failed the One-Week Assessment also failed first attempt (13/19)
  - Due to small sample size, it is unknown whether additional failures might have been observed among participants who administered dose correctly on first attempt

Device Usability: Case Study from Study 2302

- 7 year old M from Egypt, 11 kg in weight, 110 cm in height, BMI of 9 kg/m2
- Screening FEV1 0.33 L (33% predicted)
- Day 29 relative change from baseline in FEV_1% predicted **-36.7%**
- Technical evaluations of the inhalers used showed
  - **A large amount of residual powder in the capsule chamber**
  - **Partially blocked holes in the mouthpiece of used inhalers**
  - **Used capsules often pierced twice at the same end or on both ends**
  - **Signs consistent with not inhaling full capsule content**
- Serum tobramycin concentrations
  - Not quantifiable on Visit 2
  - **Low (<0.5 µg/mL) at Visit 3 (Day 29)**
- Sputum concentrations
  - Day 1 - within range with the rest of the patients*
  - Day 29 - low compared to the rest of the patients**

*920 µg/g at 0–0.5h & 312 µg/g at 0.5–2h post-dose **248, 64.4 & 84.4 µg/g for pre-dose, 0–0.5h & 0.5–2h post-dose, respectively

Device Issues

- Small numbers of inspected devices from clinical trials had caking of powder within inhaler
  - Could be moisture related, especially if IFU not followed
- Capsules dented, pierced
  - Blister package design and manufacturing process altered

Conclusions

- CF is an orphan disease for which treatment options are limited and treatment regimens burdensome
- TIP safety data exhibit potential concerns regarding increased use of antipseudomonals, increased rates of drug discontinuations, and increased local irritation relative to a currently approved drug/device combination
  - Difficult to connect one study findings with another
- Usability and device data are insufficient and portend the types of critical errors that would inhibit correct use of the drug/device combination
- The context of reducing treatment burden must be weighed carefully against these safety concerns

Acknowledgments

- Eileen Navarro-Almario- Clinical Team leader, DAIP
- Christopher Kadoorie – Statistical Reviewer, DAIP
- Aleksander Winiarski – DMEPA HF Reviewer
- Quynh Nhu Nguyen – CDRH HF Reviewer
- Ryan Owen – Clinical Pharmacology Reviewer, DAIP
- Peter Coderre – Clinical Microbiology Reviewer, DAIP
- Mark Seggel – CMC Reviewer
- Amy Ellis – Pharmacology Toxicology Reviewer, DAIP
- Christopher Davi – Project Manager, DAIP
- Robert Lim – Pulmonary Consultant, DPARP
- Katherine Laessig, Deputy Division Director, DAIP
- John Farley, Acting Division Director, DAIP

Statistical Review Perspective: Efficacy Findings for Studies C2301 and C2303

Christopher Kadoorie, Ph.D.
Statistical Reviewer
Division of Biometrics IV
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Outline

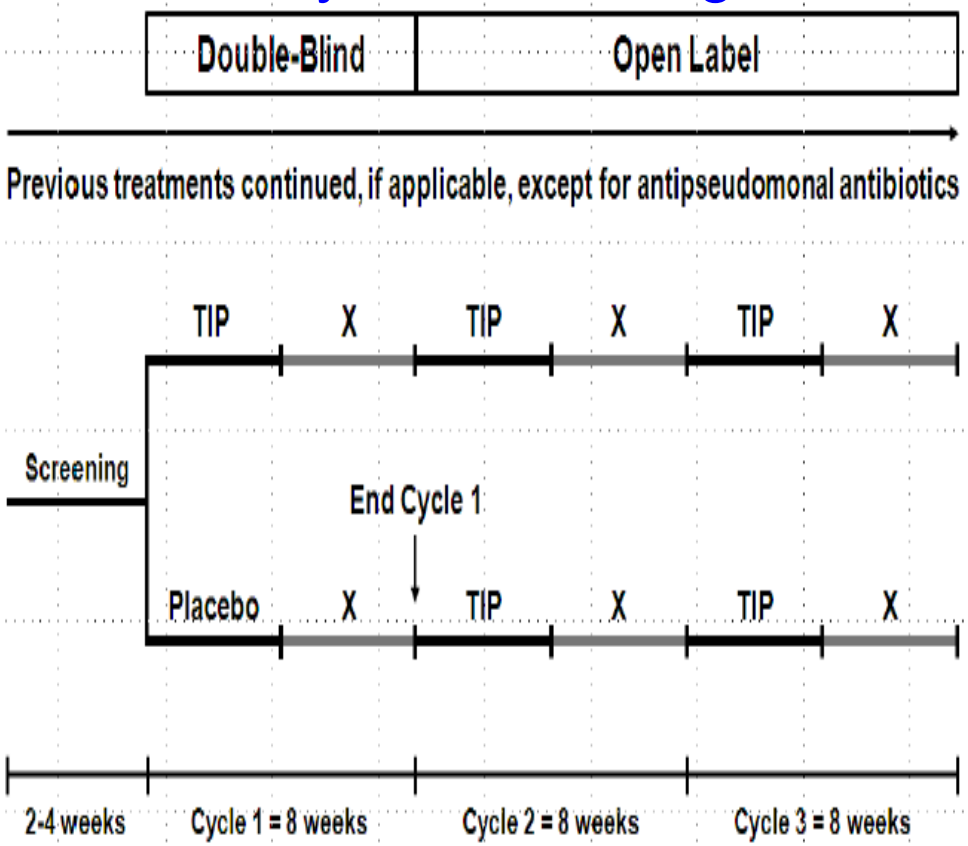
- Comparison: Studies C2301 vs. C2303
- Issues of Concern
- Efficacy Findings
  - Primary analyses
  - Sustainability of treatment effects
  - Regional effects
  - Supportive analyses
- Summary & Conclusions

Similarities: Study C2301 vs. C2303

- Both designed to demonstrate efficacy & safety of TIP (4 x 28 mg BID) vs. placebo
- Inclusion criteria were similar
- Number of patients included in the primary analysis population was similar:
  - 61 patients in Study C2301
  - 62 patients in Study C2303
- Primary endpoint was similar- the relative change from baseline in FEV1 % predicted:
  - Assessed at Day 28 in Study C2301
  - Assessed at Day 29 in Study C2303

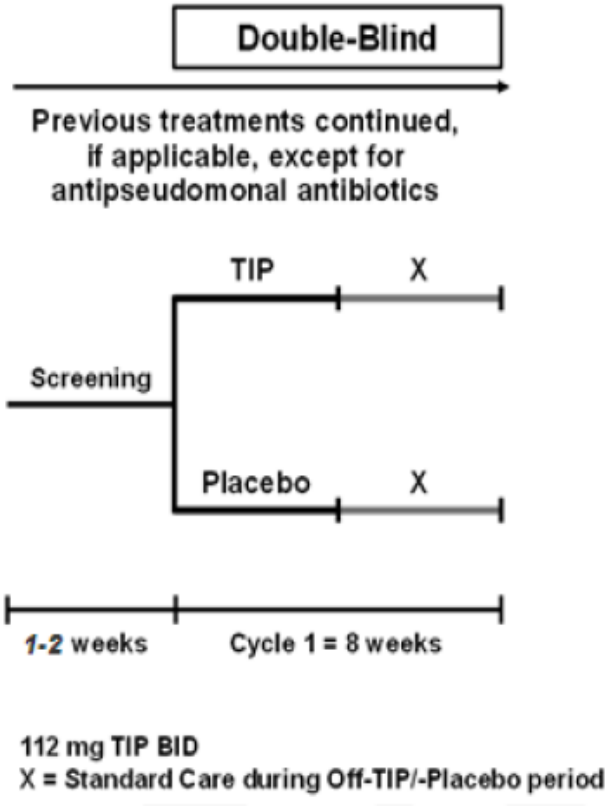
Differences: Study C2301 vs. C2303

Study C2301 Design



TIP = tobramycin inhalation powder
X = Standard of care in off-treatment period

Study C2303 Design



Source: Figures 7-1 & 7-10 in Applicant's Briefing Document

Differences: Rationale for Sample Size

	Study C2301	Study C2303
Initial Planned Sample Size:	**140 enrolled subjects**	**100 enrolled subjects**
Original Interim Analysis (OIA):	Potential for early stopping for efficacy after ~ 80 (79 actual) subjects complete Cycle 1 dosing *(Trial stopped early for efficacy based on OIA).*	No interim analyses planned.
Sensitivity Interim Analysis (SIA):	OIA later found problematic due to unreliable spirometry data in L. American sites. (SIA used instead). SIA 'repeated' the OIA removing 18 patients with faulty spirometry data. SIA was performed on 79-18=61 subjects. *(Trial stopped early for efficacy based on SIA).*	
Primary analysis population:	**61 (29 TIP, 32 Placebo)**	**62 (32 TIP, 30 Placebo)**
Rationale for sample size:	**Early stopping for efficacy while trying to ensure robust spirometry data.**	**Maximum feasible recruitment**

Differences: Patient Disposition

	Study C2301	Study C2303
Randomized:	102 (48 TIP, 54 Placebo)	62 (32 TIP, 30 Placebo)
Randomized (Treated):	**95 (46 TIP, 49 Placebo)**	**62 (32 TIP, 30 Placebo)**
Patients excluded from primary analysis population: Discontinued Had unreliable spirometry	34 (17 TIP, 17 Placebo) 16 (7 TIP, 9 Placebo) 18 (10 TIP, 8 Placebo)	**0**
Primary analysis population:	**61 (29 TIP, 32 Placebo)**	**62 (32 TIP, 30 Placebo)**
Patients excluded from primary analysis (due to missing data):	3 (2 TIP, 1 Placebo) *No Day 28 measurement*	3 (1 TIP, 2 Placebo) *No BL measurement*
Included in primary analysis:	**58 (27 TIP, 31 Placebo)**	**59 (31 TIP, 28 Placebo)**

In Study C2303, 7 patients (6 TIP, 1 Placebo) with missing outcomes (missing/faulty Day 29 measurement) were included in the primary analysis with imputed values.

Other Important Differences

- Study C2301 evaluated a *more diverse population*:
  - 15.8% non-Caucasian patients vs. 1.6% in Study C2303
  - Patients from Europe, N. America and L. America vs. Eastern Europe (primarily) in Study C2303
- Evaluated a *sicker study population* with 88% prior antibiotic use vs. 27% in Study C2303
- Evaluated a TIP formulation based on *older manufacturing process* vs. Study C2303

Issues of Concern

- Study C2301:
  - 37/95 (39%) of treated patients excluded from the primary analysis
  - Uncertain reliability of spirometry measurements
  - Regional differences in treatment effects (N. America vs. Europe)
  - Missing data at later visits
  - Unclear sustainability of treatment effects
  - Limited supportive evidence

- Study C2303:
  - The study was not successful (FDA primary analysis p-value: 0.233)
  - Inadequate supportive evidence for a positive treatment effect

FDA Primary Analysis Methodologies

- Non-parametric tests were considered because of a possible violation of normality assumptions
  - TIP distributions were positively skewed
  - TIP & Placebo arms both had several influential observations
- Parametric tests were also considered. However, variance of the primary outcome was estimated using observed cases (if missing data were substantial)
- Missing primary outcomes were imputed using the smaller of two values:
  - A value of '0' (no improvement from baseline)
  - The least favorable group mean using observed cases (no relative treatment benefit)
- Sensitivity analyses considered all randomized (treated) patients

Primary Analyses (Study C2301)

FDA Analysis	TIP (N=29)	Placebo (N=32)	Difference (95% CI)	P-value
Adjusted Mean*	12.54	0.09	12.44 (4.89, 20.00)	p=.0017 **p=.0061#x**
Unadjusted Mean (Median)	12.26 (9.52)	-0.57 (-0.29)	12.83 (5.23, 20.44)	p=.0013 p=.0052x

Applicant Analysis	TIP (N=27)	Placebo (N=31)	Difference (95% CI)	P-value
Adjusted Mean*	13.97	0.68	13.29 (5.31,21.28)	**p=.0016#**
Unadjusted Mean	13.21	-0.57	13.79 (5.87, 21.70)	p=.0010

Primary analyses in **bold #**, non-parametric tests in blue x, * ANCOVA adjusted for age, region, FEV1 % predicted at Baseline

FDA Sensitivity Analysis (Study C2301)

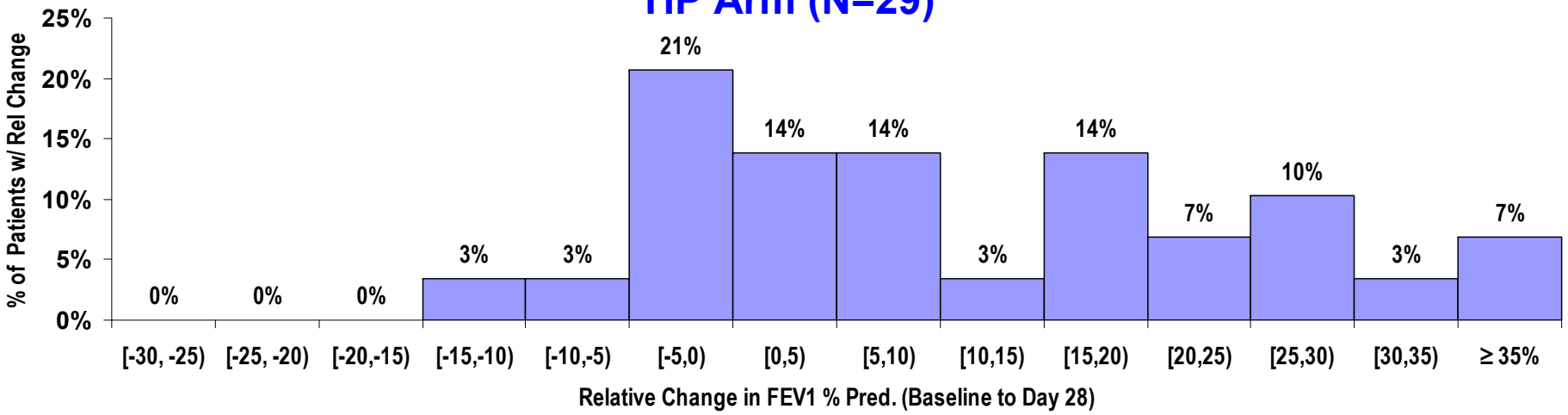
All Randomized Treated Patients	TIP (N=46)	Placebo (N=49)
Patients incl. in Applicant's Primary Analysis	27 (58.7%)	31 (63.3%)
Patients Excluded	19 (41.3%)	18 (36.7%)

FDA Sensitivity Analysis	TIP (N=46)	Placebo (N=49)	Difference (95% CI)	P-value
Adjusted Mean*	6.87	-1.26	8.14 (2.00, 14.28)	p=.009** p=.023#
Unadjusted Mean	7.52	-0.57	8.09 (1.92, 14.26)	p=.010** p=.035#

Non-parametric tests in blue #, imputation used the least favorable (placebo) mean of -0.57%, *adjusted for age & region,**Variance estimated using observed cases.

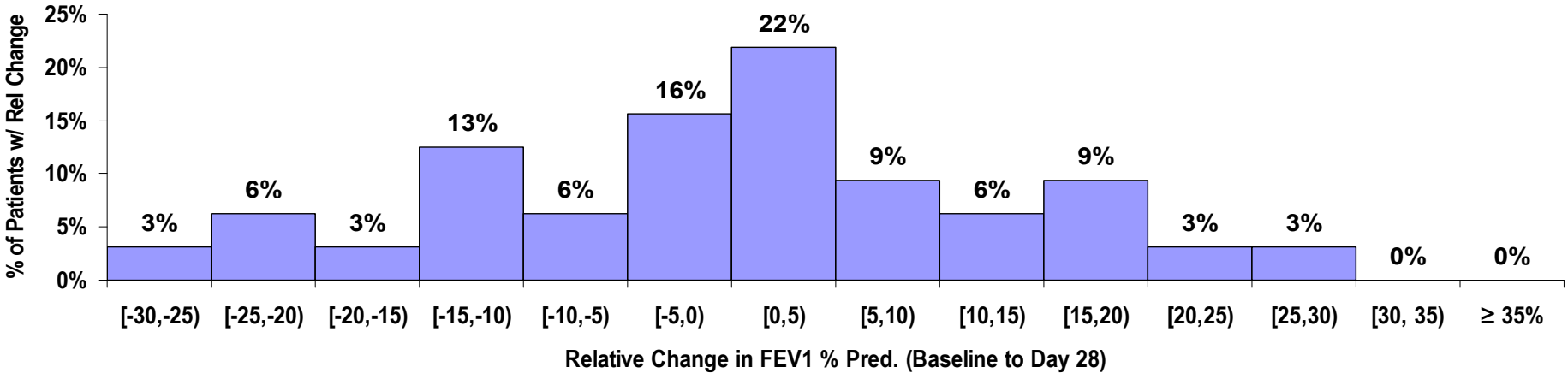
Distributions of Primary Outcome (Study C2301)

TIP Arm (N=29)



Mean =12.26%, Median=9.52%, Most favorable: 56.4%, 48.2%, Least favorable: -10.2%, -6.1%

Placebo Arm (N=32)



Mean = -0.57%, Median= -0.29%, Most favorable: 25.3%, 23.9%, Least favorable: -28.3%, -23.6%, -21.8%,-19.8%

Unclear Sustainability (Study C2301)

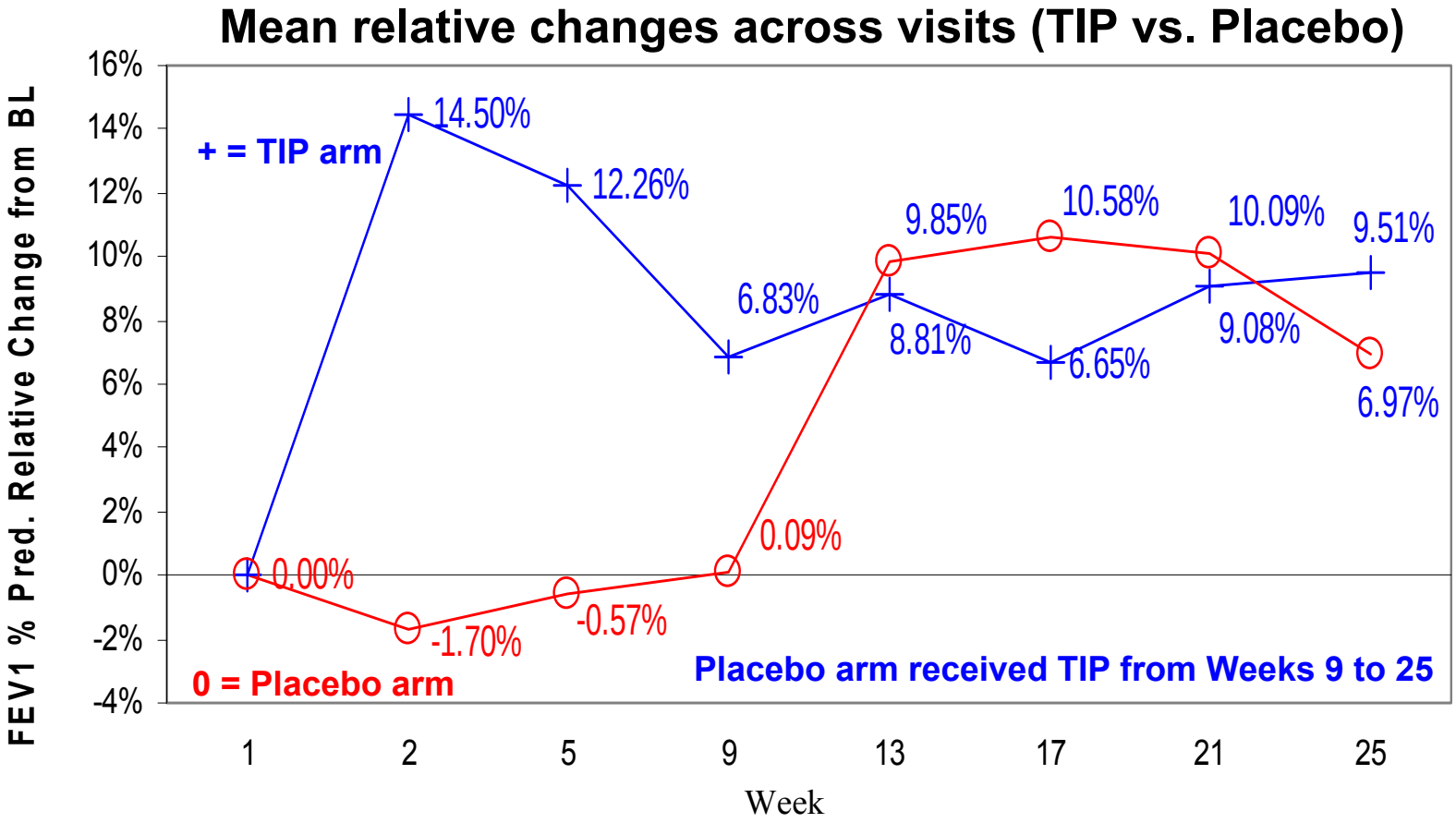
- Sustainability of primary outcome effect was considered a key factor in assessing robustness of efficacy findings.

- However, evaluation of sustainability of effects was limited by two factors:
  - Patients in placebo arm received TIP during cycles 2 & 3
  - Increased rates of missing data after Week 5

Missing Data (Study C2301)

Visit	TIP (N=29) Missing: n(%)	Placebo (N=32) Missing: n(%)
Week 2	3 (10.3%)	0
Week 5 (Primary)	**2 (6.9%)**	**1 (3.1%)**
Week 9	3 (9.4%)	5 (15.6%)
Week 13	5 (17.2%)	5 (15.6%)
Week 17	6 (20.7%)	7 (21.9%)
Week 21	6 (20.7%)	7 (21.9%)
Week 25	6 (20.7%)	8 (25.0%)

Unclear Sustainability (Study C2301) cont.



The mean treatment difference at Week 5 of 12.83% (12.26% – -0.57%) decreased to 6.73% by Week 9, a 6.1% drop.

Supportive Analyses (Study C2301)

- Supportive analyses were limited:
  - Rates of new antipseudomonal antibiotic use
  - Rates of respiratory related hospitalizations

All Randomized Safety Population	TIP (N=46) n (%)	Placebo (N=49) n (%)	Difference (95% CI) P-value
New antipseudomonal antibiotic use (Cycle 1)	6 (13.0)	9 (18.4)	-5.3 (-20.5, 10.0), p=0.477
Respiratory related hospitalizations (Cycle 1)	2 (4.4)	6 (12.2)	-7.9 (-4.0, 20.7), p=0.166

Regional Effects (Study C2301)

- Study C2301 showed a concerning trend in regional effects: Much larger relative changes in Europe vs. North America

Mean (median) relative changes from BL in FEV1 % pred. at Day 28

Study C2301	TIP (N=29)	Placebo (N=32)	Difference (95% CI), p-value
N. America N=20	1.25 (-1.90) n=9	-2.65 (-2.56) n=11	3.90 (-6.44, 14.24), p=0.438
Europe N=33	17.16 (19.25) n=17	-0.35 (1.19) n=16	17.51 (8.14, 26.89), p=0.006

8 remaining Latin American patients not shown

- Significance in the primary analysis may not be clear for the scenario of all randomized patients from N. American sites

Primary Analyses (Study C2303)

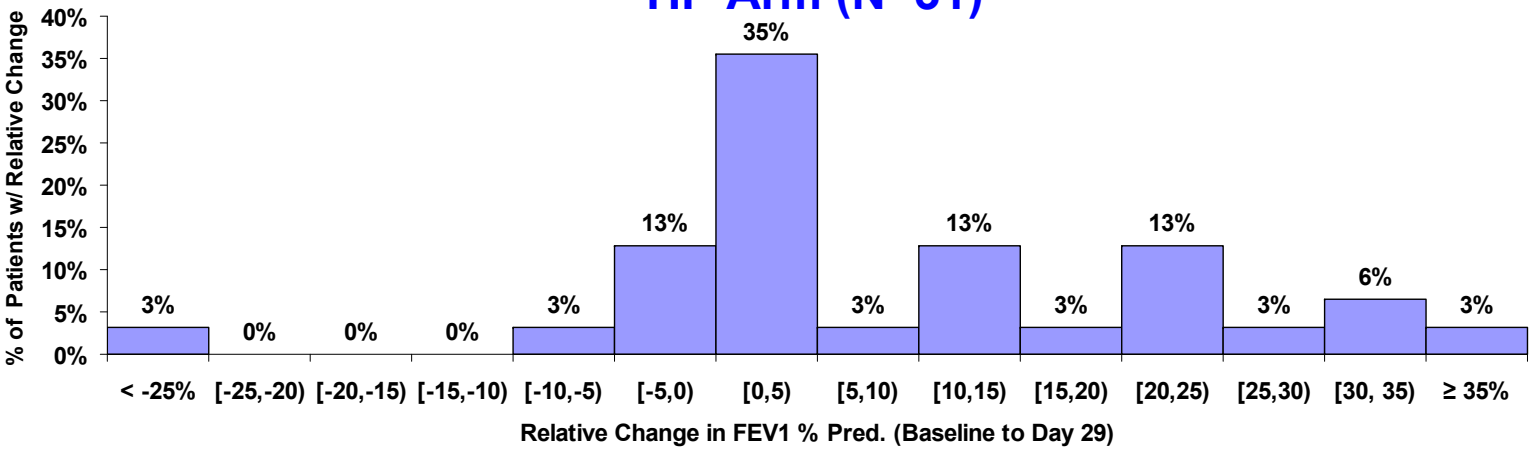
FDA Analysis	TIP (N=32)	Placebo (N=30)	Difference (95% CI)	P-value
Adj. Mean*	8.19	2.27	5.91 (-2.54,14.37)	p=.167** **p=.233#x**
Unadj. Mean (Median)	8.27 (3.17)	2.45 (2.71)	5.82 (-2.56,14.20)	p=.170** p=.244x

Applicant Analysis	TIP (N=32)	Placebo (N=30)	Difference (95% CI)	P-value
Adj. Mean*	8.2	2.3	5.9 (-2.2,14.0)	**p=.148#**
Unadj. Mean	8.3	2.4	5.8 (-2.2,13.8)	p=.151

Primary analyses in **bold #**, non-parametric tests in blue x, *adjusted for age (<13, ≥13), region, FEV1 % pred. at screening (<50%, ≥50%), **Variance estimated with observed cases

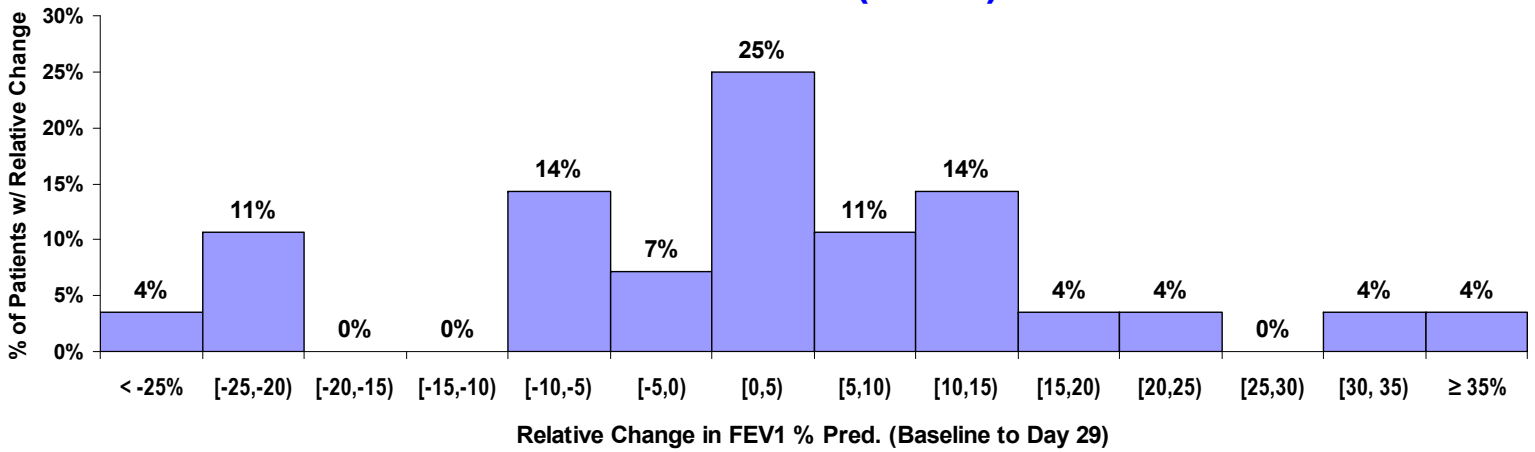
Distributions of Primary Outcome (Study C2303)

TIP Arm (N=31)



Mean=8.27%, Median=3.17%, Most favorable: 35.7%, 34.6%, 31.0%, 29.3%, Least Favorable: -36.7%, -6.9%

Placebo Arm (N=28)



Mean=2.45%, Median=2.71%, Most favorable: 38.5%, 31.7%, Least favorable: -28.3%, -23.9%, -23.5%, -22.8%

Supportive Analyses (Study C2303)

- Supportive analyses were limited:
  - Rates of new antipseudomonal antibiotic use
  - Rates of respiratory related hospitalizations

ITT Population	TIP (N=32) n (%)	Placebo (N=30) n (%)	Difference (95% CI) P-value
New antipseudomonal antibiotic use	3 (9.4)	3 (10.0)	-0.6% (-17.9,16.1)
Respiratory related hospitalizations	0 (0)	1 (3.3)	-3.3%

Summary and Conclusions

- Both Applicant & FDA primary analyses showed significance in Study C2301. However, strength of evidence depended on:
  - Consideration of all treated patients (no exclusions)
  - Consideration of non-parametric analyses
- Study C2301 also had other limitations:
  - Unreliable spirometry measurements
  - Differential regional effects (Europe vs. N. America)
  - Unclear sustainability of treatment effects
  - Inadequate supportive analyses
- Study C2303 differed from Study C2301- It was unsuccessful:
  - Could not show efficacy in the primary analysis (p=0.233).
  - Lacked supportive evidence for a positive treatment effect.
- Overall evidence of efficacy relied on 1 controlled study (w/o substantial supportive evidence from other controlled studies).

Acknowledgements

- Thamban Valappil, PhD
- Shrimant Mishra, MD
- Eileen Navarro, MD
- Mohammad Huque, PhD
- Daphne Lin, PhD

Thank you!

New Drug Application 201,688

(tobramycin inhalation powder)

Microbiology Review Perspective

Increased Tobramycin MICs and Resistance in *Pseudomonas aeruginosa* (PA) During Therapy

Peter Coderre, PhD, MBA
Clinical Microbiology Reviewer
Division of Anti-Infective Products
Anti-Infective Drugs Advisory Committee Meeting
05 September 2012

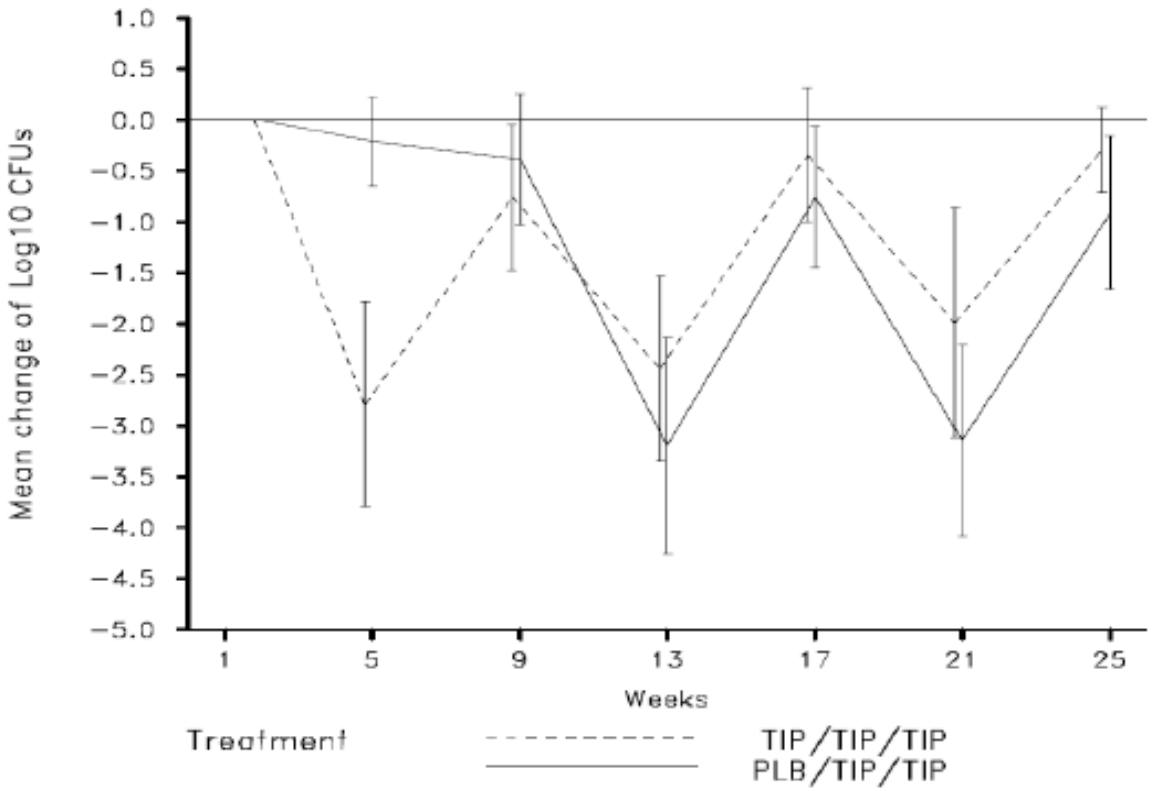
Microbiological Analyses

- Analyses during review:
  - log10 reduction rates of PA during therapy
  - Changes in MIC during therapy
  - Changes in resistance during therapy
  - Surveillance data
  - Other treatment emergent pathogens

Microbiological Analyses

- Analyses during review:
  - **log10 reduction rates of PA during therapy**
  - Changes in MIC during therapy
  - Changes in resistance during therapy
  - Surveillance data
  - Other treatment emergent pathogens

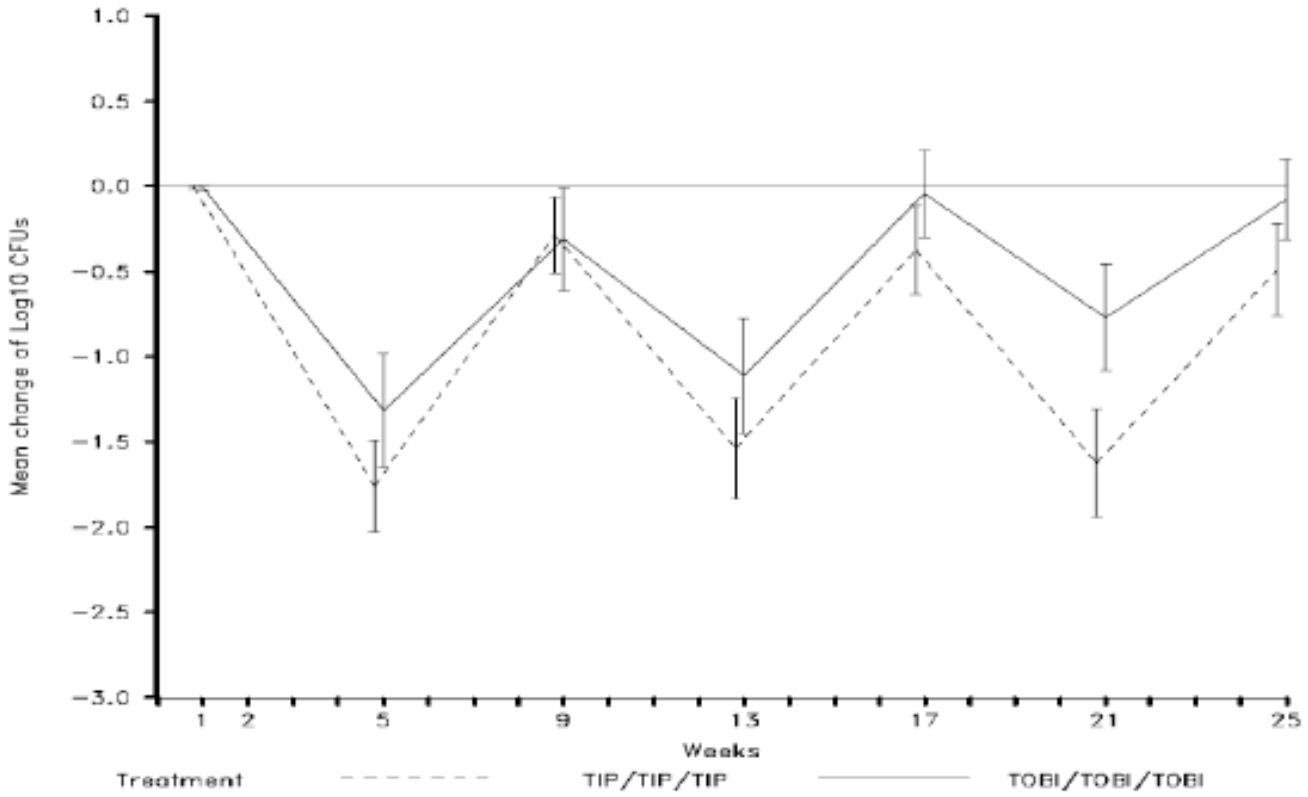
Change from Baseline in *P. aeruginosa* Sputum Density (Log10 CFUs) in Cycles 1 to 3; Study C2301 (ITT Population)



Note: the vertical bar is 95% confidence interval.
Overall density is used, and it is defined as the sum of bio-types (mucoid, dry and small colony variant).

Source: Figure 4-6, Clinical Pharmacology Summary, NDA 201,688 (this submission).

Between Treatment Comparison of Change in *P. aeruginosa* Sputum Concentration (Log10 CFU) – Study C2302 (ITT Population)



Note: the vertical bar is 95% confidence interval. Overall density is used, and it is defined as the sum of colony types (mucoid, dry and small colony variant).
Source: Figure 4-7, Clinical Pharmacology Summary, this submission.

Microbiological Analyses

- Analyses during review:
  - log10 reduction rates of PA during therapy
  - **Changes in MIC during therapy**
  - Changes in resistance during therapy
  - Surveillance data
  - Other treatment emergent pathogens

Interpretive Criteria

Systemic Tobramycin CLSI* Breakpoints for *Pseudomonas aeruginosa*:

Susceptible: ≤ **4 mcg/ml**

Intermediate: **8 mcg/ml**

Resistant: ≥ **16 mcg/ml**

***Clinical and Laboratory Standards Institute**

MIC Summary for Study C2301, Maximum of All Colony Types

	Tobramycin MIC (µg/mL)							
	TIP/TIP/TIP				placebo/TIP/TIP			
Range	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90
Baseline	44	≤0.25->512	0.5	32	48	≤0.25->512	1	8
Week 5	29	≤0.25->512	1	>512	44	≤0.25-8	0.5	2
Week 21	28	≤0.25->512	1	>512	30	≤0.25-256	1	32
Week 25	30	≤0.25->512	1	128	37	≤0.25->512	1	8
Termination	40	≤0.25->512	1	32	48	≤0.25->512	1	8

Color code: yellow=two dilution step increase over baseline; orange=three dilution step increase over baseline; red=four dilution step increase over baseline; blue=two dilution step decrease versus baseline; purple=three or more dilution step decrease versus baseline; green= two or more dilution step difference between MIC90 values for baseline study arms.

Source: Table 4-13, Clinical Pharmacology Summary, this submission.

MIC Summary for Study C2302, ITT Population; Maximum of All Colony Types

	Tobramycin MIC (µg/mL)							
	TIP				TOBI			
Range	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90
Baseline	308	≤0.12->512	2	64	208	≤0.12->512	2	128
Week 5	239	≤0.12->512	2	512	173	≤0.12->512	4	64
Week 21	199	≤0.12->512	4	256	154	≤0.12->512	4	256
Week 25	201	≤0.12->512	2	256	155	≤0.12->512	2	64
Termination	298	≤0.12->512	2	512	202	≤0.12->512	2	64

Color code: yellow=two dilution step increase over baseline; orange=three dilution step increase over baseline; red=four dilution step increase over baseline; blue=two dilution step decrease versus baseline; purple=three or more dilution step decrease versus baseline; green= two or more dilution step difference between MIC90 values for baseline study arms.
Source: Table 4-18, Clinical Pharmacology Summary, this submission.

Microbiological Analyses

- Analyses during review:
  - log10 reduction rates of PA during therapy
  - Changes in MIC during therapy
  - **Changes in resistance during therapy**
  - Surveillance data
  - Other treatment emergent pathogens

P. aeruginosa Tobramycin MIC Increase by Colony Type, Study C2301

Colony type	% increase by treatment arm	
	TIP/TIP/TIP N=46	Placebo/TIP/TIP N=49
dry colony	7.6%	7.2%
mucoid colony	5.4%	4.3%
small colony	18.6%	0%
maximum of MIC colony types per patient	8.6%	0%

Source: Table 3.2-1.6, this submission.

Tobramycin Resistance Increase by *P. aeruginosa* Colony Type, Study C2302

Colony type	% increase by treatment arm	
	TIP N=308	TOBI N=209
dry colony	6.7%	- 4.3%
mucoid colony	7.3%	- 1.4%
small colony	18.4%	- 6.7%
maximum of MIC colony types per patient	7.8%	- 2.3%

Source: Table 14.2-3.3, this submission.

Antibiotic Resistance Increase by *P. aeruginosa* Colony Type, Study C2302

	% increase in antibiotic resistance by treatment arm	
antibiotic/colony type	**TIP**	**TOBI**
aztreonam		
dry colony	1.3%	6.3% ←
mucoid colony	3.7%	1.9%
small colony	4.0%	- 2.5%
mixed colony types	4.7%	3.6%
ceftazidime		
dry colony	- 2.3%	2.8%
mucoid colony	5.9% ←	-0.2%
small colony	3.5%	8.9% ←
mixed colony types	3.0%	-2.1%
ciprofloxacin		
dry colony	7.1%	5.5%
mucoid colony	7.3% ←	- 0.2%
small colony	3.5%	7.9%
mixed colony types	9.1% ←	4.4%
imipenem		
dry colony	0.8%	4.7%
mucoid colony	1.1%	3.2%
small colony	-16.3%	- 0.4
mixed colony types	0.5%	5.8% ←
meropenem		
dry colony	- 0.9%	1.2%
mucoid colony	6.5% ←	0.8%
small colony	- 2.3%	- 2.8%
mixed colony types	3.6%	1.0%

Source: Table 14.2-3.4, this submission.

Evidence of increased tobramycin resistance in the TIP arm compared to TOBI arm (C2302)

	Cycle 1, Day 1		Cycle 1, Day 28	
	TIP (n=292)	TOBI (n=200)	TIP (n=239)	TOBI (n=173)
Percentage of subjects with MIC ≥ 16 µg/mL	23% (n=69)	23% (n=46)	30% (n=71)	25% (n=43)
Percentage of subjects with MIC ≥ 64 µg/mL	12% (n=35)	14% (n=28)	21% (n=50)	12% (n=20)

- An increase in tobramycin resistance was observed in the TIP arm as compared to the TOBI arm in Study C2302
  - Similar distribution at baseline, but an increase in resistance at the end of cycle 1
  - Due to the limited number of subjects with PK data available, we can not determine whether a decrease in exposure (systemic or sputum) contributed to this increased tobramycin resistance

Evidence of Increased Tobramycin Resistance in the TIP Arm Compared to TOBI Arm (C2302)

	Cycle 1, Day 28 and Baseline MIC <16 µg/mL	
	TIP (n=184)	TOBI (n=134)
Percentage of subjects with MIC ≥ 16 µg/mL	21% (n=39)	12% (n=16)
Percentage of subjects with MIC ≥ 64 µg/mL	14% (n=25)	4% (n=5)

- An increase in tobramycin resistance was observed in the TIP arm as compared to the TOBI arm in Study C2302
  - Similar distribution at baseline, but an increase in resistance at the end of cycle 1
  - Due to the limited number of subjects with PK data available, we can not determine whether a decrease in exposure (systemic or sputum) contributed to this increased tobramycin resistance
- Subjects with MIC <16 µg/mL in the TIP treatment arm were more likely to develop tobramycin resistance by the end of cycle 1

Microbiological Analyses

- Analyses during review:
  - log10 reduction rates of PA during therapy
  - Changes in MIC during therapy
  - Changes in resistance during therapy
  - **Surveillance data**
  - Other treatment emergent pathogens

Surveillance Data: 1999-2009

- **Shawar et al. (1999)**
  - **Tobramycin resistance: 5.4%; mucoid 2.4%, non-mucoid 9.4%**
- **14 studies, 2/14 recently (last 3 years), both outside US**
  - **8/14 studies, MIC90 => 16 mcg/ml; range 16 mcg/ml to >1024 mcg/ml**
  - **5/14 studies, => 10% resistance; range 10% to 52%**
  - **resistance worldwide: US, Germany, UK, Spain, Japan**

Although data limited, tobramycin resistance in PA from CF patients has nearly doubled since 1999, an increase of more than 85%

Microbiological Analyses

- Analyses during review:
  - log10 reduction rates of PA during therapy
  - Changes in MIC during therapy
  - Changes in resistance during therapy
  - Surveillance data
  - **Other treatment emergent pathogens**

Treatment-emergent Organisms Present in More Than One Patient in Pooled Data- Study C2301 and C2303

57 isolates from 78 (73%) TIP patients; 45 isolates from 79 (57%) placebo patients

More than 50% of patients had emergent organisms

16% more emergent isolates from TIP patients

Organism	No. Isolates[a]	
	TIP[b]	Placebo[c]
Bacteria		
Achromobacter xylosoxidans	2	0
Alcaligenes faecalis	2	0
Chryseobacterium indologenes	0	2
Haemophilus influenzae	7	2 ←
Haemophilus parainfluenzae	6	8
Serratia marcescens	1	4
Staphylococcus aureus (methicillin-resistant)	1	2
Staphylococcus aureus (methicillin-sensitive)	6	6
Stenotrophomonas maltophilia	4	2 ←
β-hemolytic Streptococcus, Group A	2	1
β-hemolytic Streptococcus, Group B	2	1
β-hemolytic Streptococcus, Group C	2	1
β-hemolytic Streptococcus, Group G	2	0
Streptococcus pneumoniae	1	3
Yeasts and Fungi		
Candida albicans	2	0 ←
Aspergillus fumigatus	3	4
Penicillium species	4	0 ←
Filamentous mold other than *Penicillium/Aspergillus*	2	2

a Total number of isolates for End of Dosing and End of Cycle 1
b No. patients = 78
c No. patients = 79
Source: Table 4-37 [SCE-Appendix 1-Table 3.4-1.10], this submission.

Summary

- ***Low*** **log10 reduction rates of *P. aeruginosa* CFUs in sputum during therapy**
- ***Large increases*** **in tobramycin MICs for *P. aeruginosa* clinical isolates during therapy**
- ***Increased resistance*** **to tobramycin and other antibiotics develop during therapy**
- **Surveillance data indicates *a near doubling of tobramycin resistance rate***
- ***Increased emergence*** **of other pathogens during therapy**

Conclusions

- Efficacy: There is no clear cut correlation between microbiological and clinical outcome. Increased MICs and resistance may have consequences for treatment outcome.

- Safety: There are strong concerns that less susceptible or resistant bacteria may be transmitted to others in the immediate environment of the CF patient. Increased emergent pathogens is a concern but limits interpretation.

An Early Warning

Pitt et al. (2003): 10% tobramycin resistance; 3.1% colistin resistance

"The level of resistance to front line antipseudomonal agents, with the exception of colistin, is disturbingly high. The prudent use of antimicrobial drugs and closer monitoring of accumulation of resistant strain populations should be actively considered."

Pitt TL et al. 2003. Survey of resistance of *Pseudomonas aeruginosa* from UK patients with cystic fibrosis to six commonly prescribed antimicrobial agents. Thorax. 58:794-6.

Backup Slide Shown at Meeting

MIC summary for Study C2302, ITT Population; Dry Colony Type

	Tobramycin MIC (µg/mL)							
	TIP				TOBI			
Range	N	Range	MIC50	MIC90	N	Range	MIC50	MIC90
Baseline	214	≤0.12->512	2	64	144	≤0.12->512	2	128
Week 5	126	≤0.12->512	4	512	99	≤0.12->512	4	128
Week 21	107	0.25->512	8	512	81	0.25->512	8	256
Week 25	118	≤0.12->512	4	512	96	≤0.12->512	2	64
Termination	225	≤0.12->512	4	512	166	≤0.12->512	2	128

Color code: yellow=two dilution step increase over baseline; orange=three dilution step increase over baseline; red=four dilution step increase over baseline; blue=two dilution step decrease versus baseline; purple=three or more dilution step decrease versus baseline; green= two or more dilution step difference between MIC90 values for baseline study arms.
Source: Table 4-16, Clinical Pharmacology Summary, this submission.