Tobramycin Inhalation Powder (TIP)

NDA 201,688

FDA Anti-Infective Drugs Advisory Committee Meeting

Novartis Pharmaceuticals Corporation

Introduction and Background

Robert Kowalski, PharmD

Global Head, Drug Regulatory Affairs

US Head of Development

Novartis Pharmaceuticals Corporation

TOBI® (tobramycin inhalation solution, USP)

Nebulized solution marketed by Novartis

- **Approved by FDA in 1997 for management of CF patients with *P. aeruginosa* – a cornerstone of CF therapy**
- **Achieves high antibiotic concentration in airways with minimal systemic exposure**
- **Approved and marketed in 43 countries**
- **Well-established efficacy and safety profile**

Tobramycin Inhalation Powder (TIP)

A new treatment option for inhaled tobramycin therapy in CF

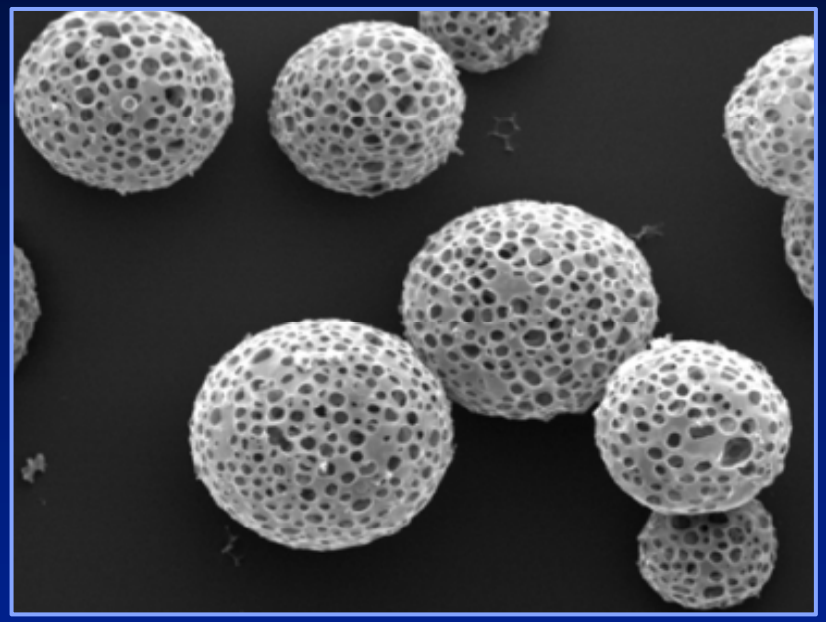
TIP is a dry powder capsule formulation of tobramycin for inhalation using the T-326 inhaler (Podhaler)

Proposed indication: management of cystic fibrosis patients with *P. aeruginosa*

TIP – Developed to Meet an Unmet Medical Need

- TIP was developed to meet a medical need to relieve the high treatment burden and improve patient adherence in CF
- TIP is a different formulation of TOBI and provides comparable efficacy and safety
- TIP improves on TOBI by making tobramycin delivery faster and more portable

Porous Tobramycin Particles Allow for "mg-scale" Drug Delivery

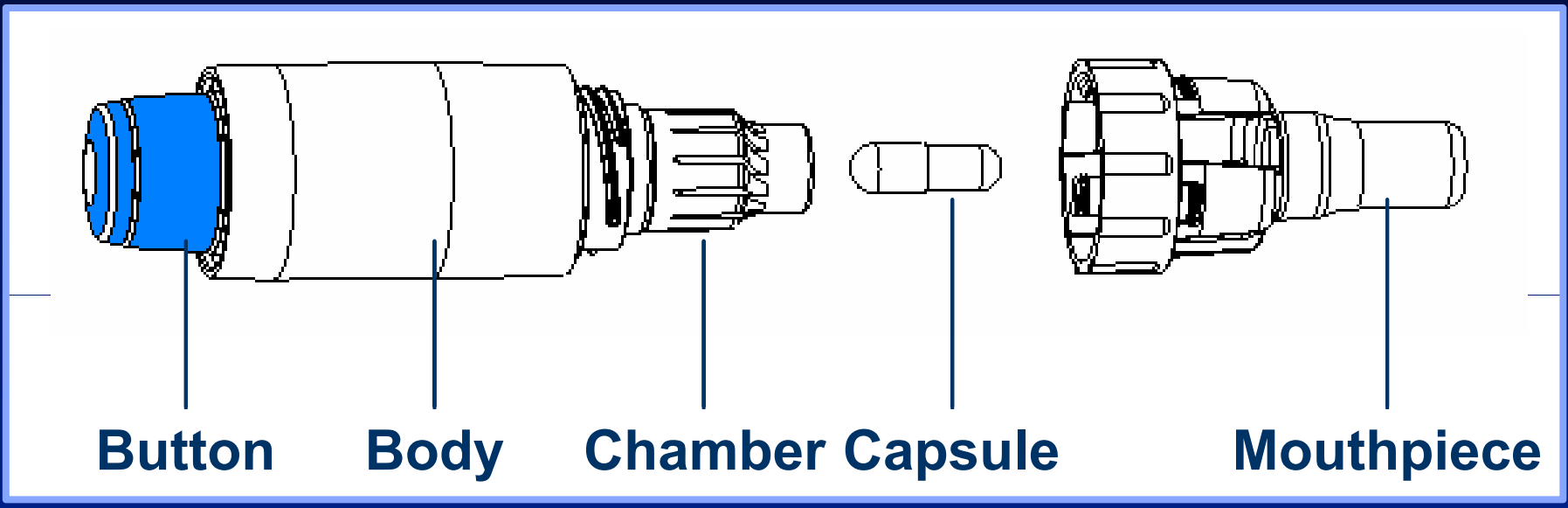


Hollow PulmoSphere™ tobramycin particles fluidize and disperse well in the inhaled airstream

PulmoSphere™ technology enables a larger percentage of drug to bypass the oropharynx and reach the lungs

T-326 Inhaler – a Dry Powder Inhaler

Basic use steps and characteristics



- Requires a few simple steps: patient puts capsule into inhaler, pierces capsule by pressing blue button, inhales twice, and repeats for the dose of 4 capsules
- Wipe with dry cloth to clean; new inhaler every 7 days
- Low to medium resistance device: can also be used by patients with limited inspiratory capacity and young children

Video Demonstration

TIP

TOBI

	TIP	TOBI
Time per dose	5.6 minutes	19.7 mins + 15-20 mins setup/breakdown
Device maintenance	Wipe mouthpiece with dry cloth/ fresh inhaler every 7 days	Nebulizer cleaning/ disinfection; compressor filter change
Storage conditions	Room temperature	Refrigeration
Power source	Not needed	Needed

US Simulated Use Validation Study Results

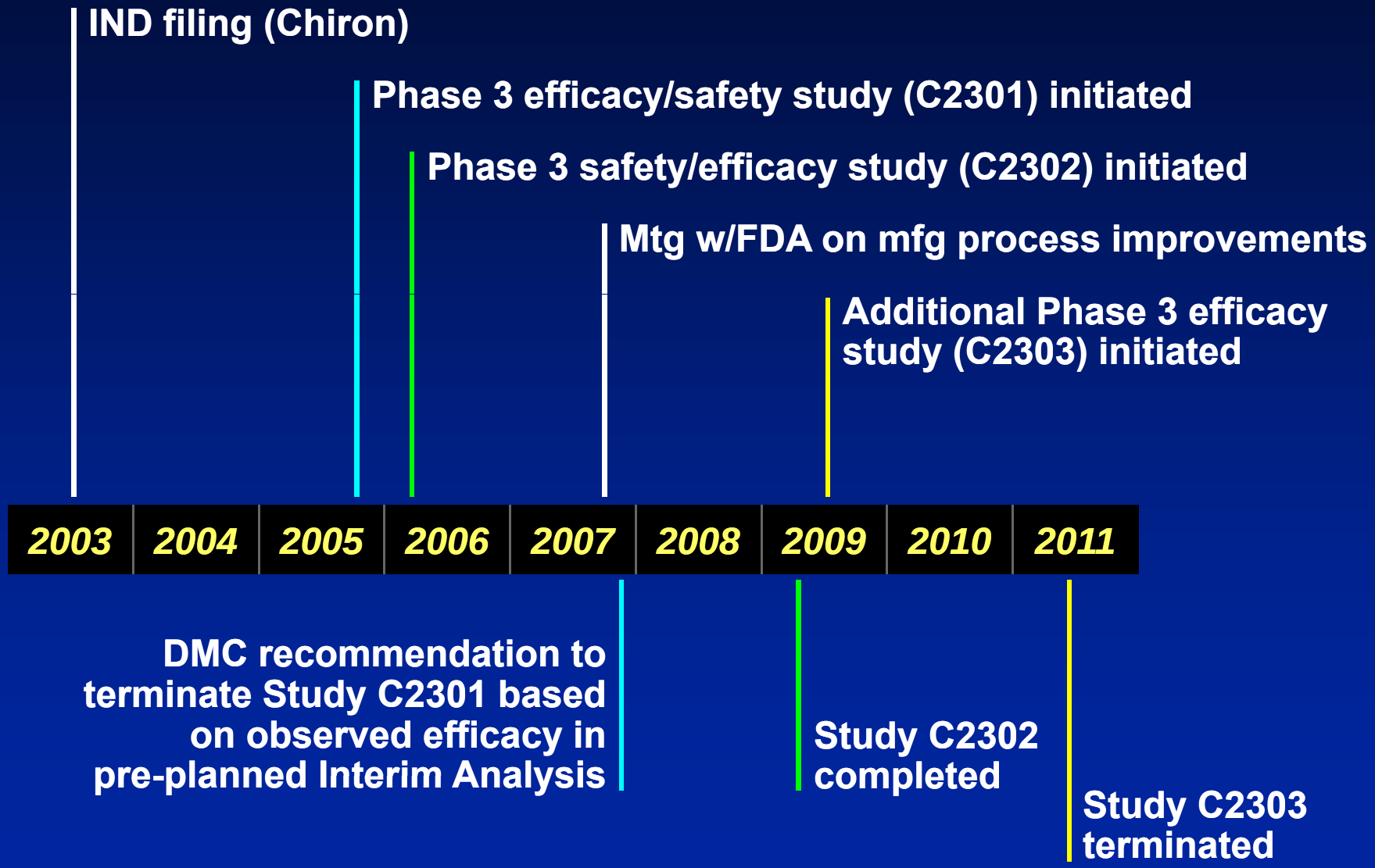
Performed in 62 patients aged 6-66 years

- **>95% demonstrated use of all 4 capsules (1 full dose), regardless of age (100% after 1 week use)**
- **Few errors observed (e.g. not exhaling fully prior to inhalation, misorientation during piercing, not checking capsule was pierced)**
- **82% rated inhaler easier to use than nebulizer**
- **Inhaler users (CF patients):**
  - **Are experienced with use of different devices**
  - **Will receive in-depth training**
- **In contrast to nebulizer, T-326 inhaler requires only a few simple steps and no extensive cleaning and disinfecting**

TIP – Proposed Dose and Usage

- Inhalation of the contents of four 28 mg capsules (112 mg) twice daily for 28 days
- TIP is administered in alternating periods of 28 days on treatment and 28 days off treatment
- Other aspects of usage (age, lung function range) similar to that of TOBI

US Regulatory and Development History



Overall TIP Manufacturing Process

Formulation (tobramycin + excipients)

Spray Drying

Emulsion is spray-dried to produce porous particles

Capsule filling

Blistering

Packaging

Improvement to Spray Drying Step

- No changes to qualitative or quantitative composition
- No clinically meaningful changes to aerodynamic particle size profile or other physicochemical properties

TIP Global Regulatory Status

- Approved in 38 countries (on basis of Studies C2301 and C2302, and comparative technical data)
  - European Union, Canada, Switzerland, Australia, Chile, Colombia, Argentina, Israel, Russia*, Venezuela
- Launched
  - Canada, Austria, Czech Republic, Denmark, Estonia, France, Finland, Germany, Ireland, Italy, Latvia, Malta, Netherlands, Norway, Portugal, Sweden, Switzerland, UK, Israel, Colombia, Argentina

* C2303 data included in dossier

TIP Is an Effective and Safe Treatment Option That Should be Available to CF Patients

- Phase 3 development program built on the experience of TOBI
- Totality of evidence supports approval of this new formulation and method of delivery
- Same active ingredient, inhaled route of administration, and indication as TOBI
- Reduces hospitalizations and use of new anti-pseudomonal antibiotics
- Potential increase in adherence to treatment
- Less burdensome and time-saving treatment option that is highly needed in this Orphan Disease population

Presentation Overview

Introduction and Background	***Robert Kowalski, PharmD*** Global Head, Drug Regulatory Affairs US Head of Development Novartis Pharmaceuticals Corporation
Unmet Medical Need in Cystic Fibrosis	***Bonnie Ramsey, MD*** Professor of Pediatrics University of Washington School of Medicine
Dose Selection and Efficacy	***Olga Santiago, MD*** Clinical Science Unit Head Novartis Pharmaceuticals Corporation
Safety and Benefit Risk	***Linda Armstrong, MD*** Therapeutic Area Safety Lead Novartis Pharmaceuticals Corporation
Clinical Perspective	***Patrick Flume, MD*** Professor, Pulmonary and Critical Care Medicine Medical University of South Carolina

Additional Experts

- **Michael Boyle, MD, FCCP**
  Director, Johns Hopkins Adult Cystic Fibrosis Program
- **Julian Dixon**
  Director of Human Factors, Team Consulting Limited
- **Barry Plant, MD**
  Director, Adult CF Center, Cork University Hospital, Ireland
- **Lisa Saiman, MD, MPH**
  Professor, Clinical Pediatrics, Pediatric Infectious Diseases
  Columbia University Medical Center
- **Lee-Jen Wei, PhD**
  Professor of Biostatistics, Harvard School of Public Health

Unmet Medical Need in Cystic Fibrosis

Bonnie Ramsey, MD

Director
CFF Therapeutics Development Network Coordinating Center

Professor of Pediatrics
University of Washington School of Medicine

Presenter Disclosure

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

- In my capacity as Director of the Cystic Fibrosis Foundation (CFF) Therapeutics Development Network Coordinating Center (TDNCC), I have received grants from the following companies in the past 3 years:

AlgiPharma AS
Amgen, Inc.
Aradigm Corporation
Axcan Pharma, Inc.
Bayer Healthcare AG
Chiesi Pharmaceuticals Inc.
CSL Behring L.L.C.
Gilead Sciences
GlaxoSmithKline
Inspire Pharmaceuticals, Inc.
KaloBios
MerLion Pharmaceuticals GmbH
Mpex Pharmaceuticals, Inc.
MPM Asset Management LLC
N30 Pharmaceuticals, LLC
Novartis Pharmaceuticals Corp.
Pharmaxis Ltd.
PTC Therapeutics, Inc.
Solvay Pharmaceuticals, Inc.
Insmed, Inc.
Vectura Ltd.
Vertex Pharmaceuticals Incorporated

- I also receive grant funding from CFF and the NIH
- I am a co-inventor on the patent for TOBI®

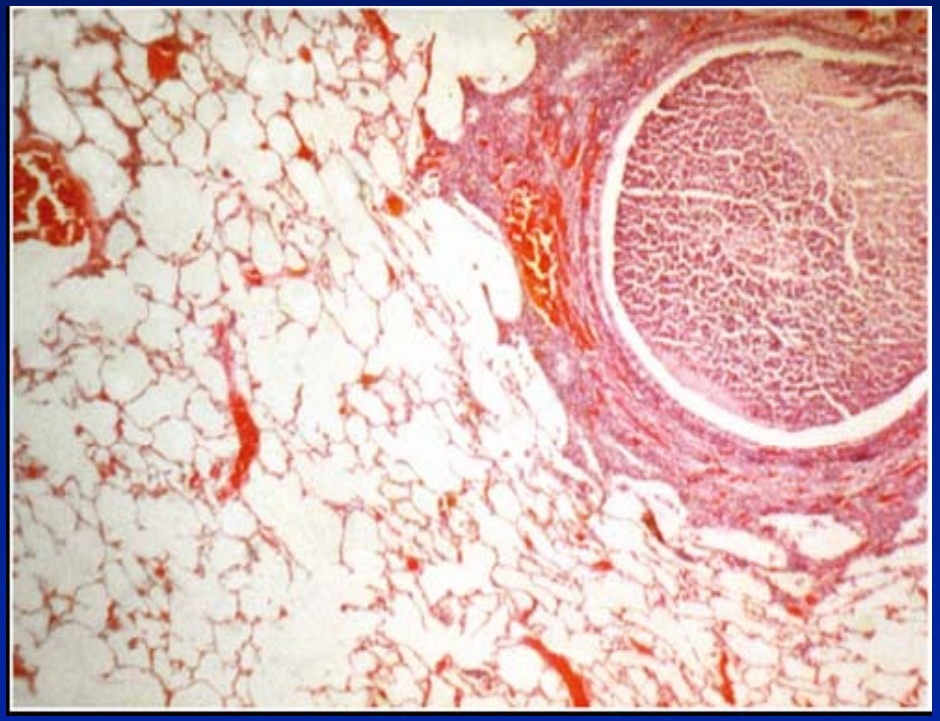
What Is CF?

- One of the most common lethal genetic diseases with a higher prevalence in Caucasians (~1:3500 Caucasian births)[1]
- Approximately 30,000 diagnosed patients in the US, 70,000 worldwide[1]
- Most patients are diagnosed shortly after birth
- With improved care and therapies adults now represent >50% of the CF population[1]

[1] Cystic Fibrosis Foundation Patient Registry, 2010 Annual Data Report. Bethesda, Maryland

What Causes CF Lung Disease?

- Caused by mutation in CFTR gene
- Results in thick, sticky mucus secretions
- Lungs most severely affected organ[1]
  - Accounts for 75% of hospitalizations and 90% of CF deaths



Am J Respir Crit Care Med, April 2012, 185: 887-892

[1] Orenstein, DM. Cystic Fibrosis: A Guide for Patient and Family

Pseudomonas aeruginosa (Pa)

- **Predominant Bacteria in CF Airways in Adulthood[1]**
- **Usually transitions to a chronic biofilm infection[2]**

Figure 1

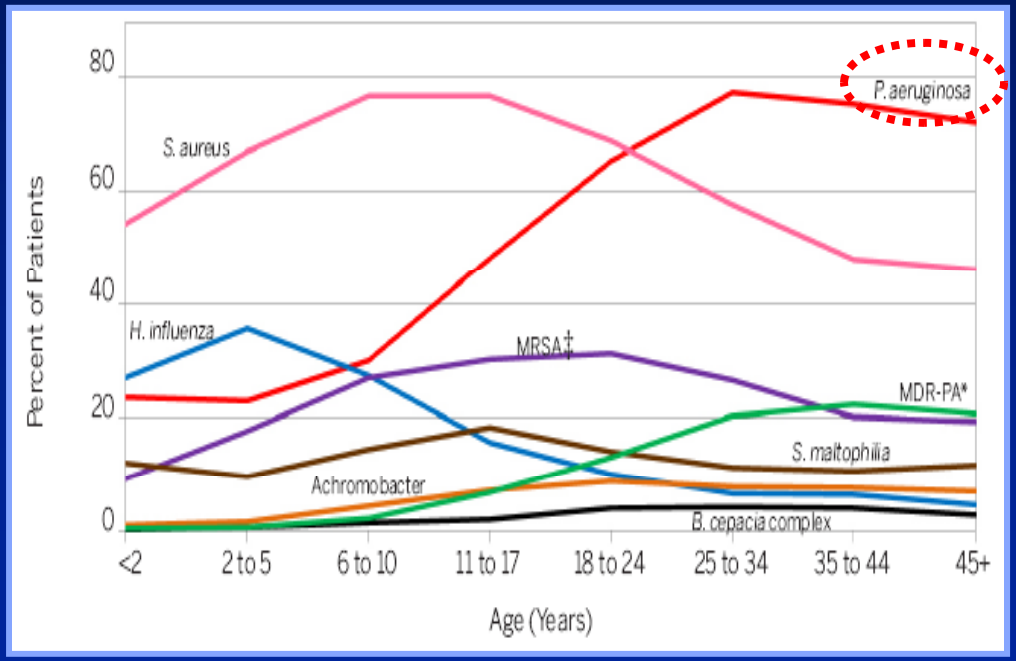
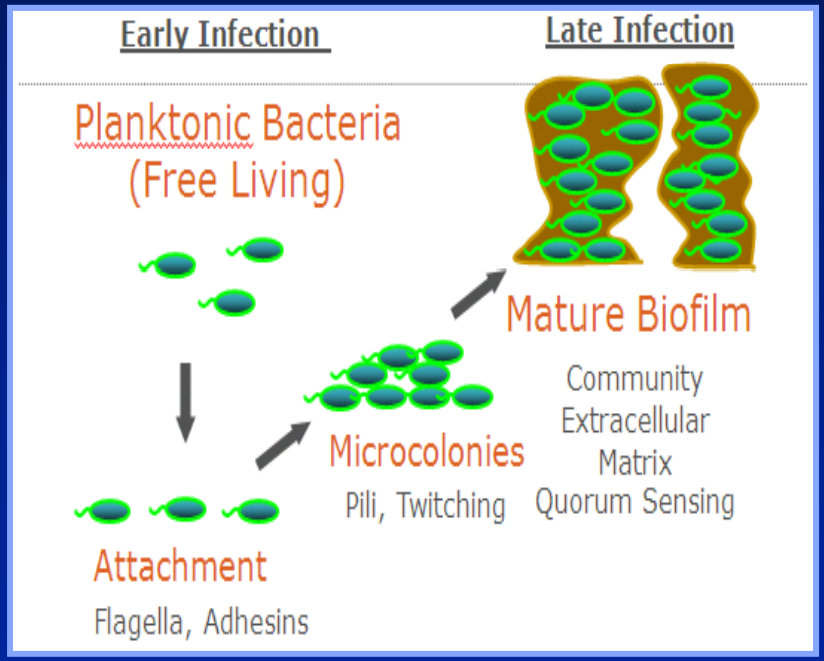


Figure 2



[1] Cystic Fibrosis Foundation Patient Registry, 2010 Annual Data Report. Bethesda, Maryland

[2] Singh, P.K., BioMetals 17: 267-270, 2004

Pa Has Major Impact on Health of CF Patients

- *Pa* is a major predictor of morbidity and mortality even in the first decade of life[1]
  - 8 year risk of death 2.6 times higher with *Pa*
- Results in more rapid lung function decline as measured by FEV_1[1]
- Causes increased rates of pulmonary exacerbation resulting in hospitalizations[1]
- Impacts patients' daily lives
  - Increased intensity and frequency of cough
  - Fatigue
  - Anorexia
  - Work/school absenteeism

[1] Emerson, J et al. Ped Pulm 2002; 34:91-100

Chronic Management of *Pa*: Inhaled Tobramycin

- CF Treatment Guidelines[1]
- Strongly recommends chronic use of inhaled tobramycin
- Received highest Grade A recommendation
- Indication to improve lung function, reduce pulmonary exacerbations and hospitalizations
- Eligible patient population
  - Age >6 years
  - Moderate to severe lung disease
  - *Pa* persistently present in cultures of the airways

[1] Flume PA, et al. *Am J Respir Crit Care Med.* 2007;176:957-969.

There is a Lack of Correlation Between MICs and Clinical Outcomes

- The relationship between *in vitro* susceptibility test results and clinical outcome for oral[1], inhaled[2,3] and intravenous[4,5] anti-pseudomonal antibiotics are not clear
- Susceptibility breakpoints established for parenteral tobramycin (8 µg/mL) do not apply to aerosolized administration of TOBI[2,3]
  - In the pivotal TOBI trials FEV_1 improved even in patients with MICs ≥128 µg/mL[3]

[1] Saiman, L. et al, JAMA 2003; 290:1749-56
[2] Ramsey, B. et al, NEJM 1999; 340:23-30
[3] Moss, R. et al, Chest 2001; 120:107S-113S
[4] Smith, A. et al, Chest 2003; 123:1495-1502
[5] Hurley et al, Journal of CF 2012; 11: 288-292

Lives of CF Patients Revolve Around Time Consuming Treatment Regimen

Regimen	Morning	Afternoon	Evening
Fat soluble vitamins	✓	–	–
Anti-inflammatory therapies	2x/day-3x/week	–	–
Enzymes with each snack/meal	8-10 per meal	8-10 per meal	8-10 per meal
*Nebulized bronchodilators	15-20 min/ treatment	–	15-20 min/ treatment
Airway Clearance	20 min/ treatment	–	20 min/ treatment
*Nebulized mucolytics	15-20 min/ treatment	–	15-20 min/ treatment
*Inhaled antibiotic	Up to 20 min/ treatment	4 min/ treatment	Up to 20 min/ treatment

* Does not include time to clean equipment which is 20 min/treatment

Current Treatments Lead to Low Adherence

Treatment	Adherence
NEBULIZED MEDS	
Self-Report[1]	80%
Daily phone diary[1]	47.6%
Prescription Refill[1]	68%
Pharmacy Claims Data for tobramycin inhalation solution[2]	6% of patients receive >4 cycles per year

[1] Modi A, et al. *Journal of CF* 2006; 177-185

[2] Briesacher BA, et al. *BMC Pulmonary Medicine 2011 11:5*.

Poor Adherence Leads to Increased Hospitalization Risk and Treatment Failure

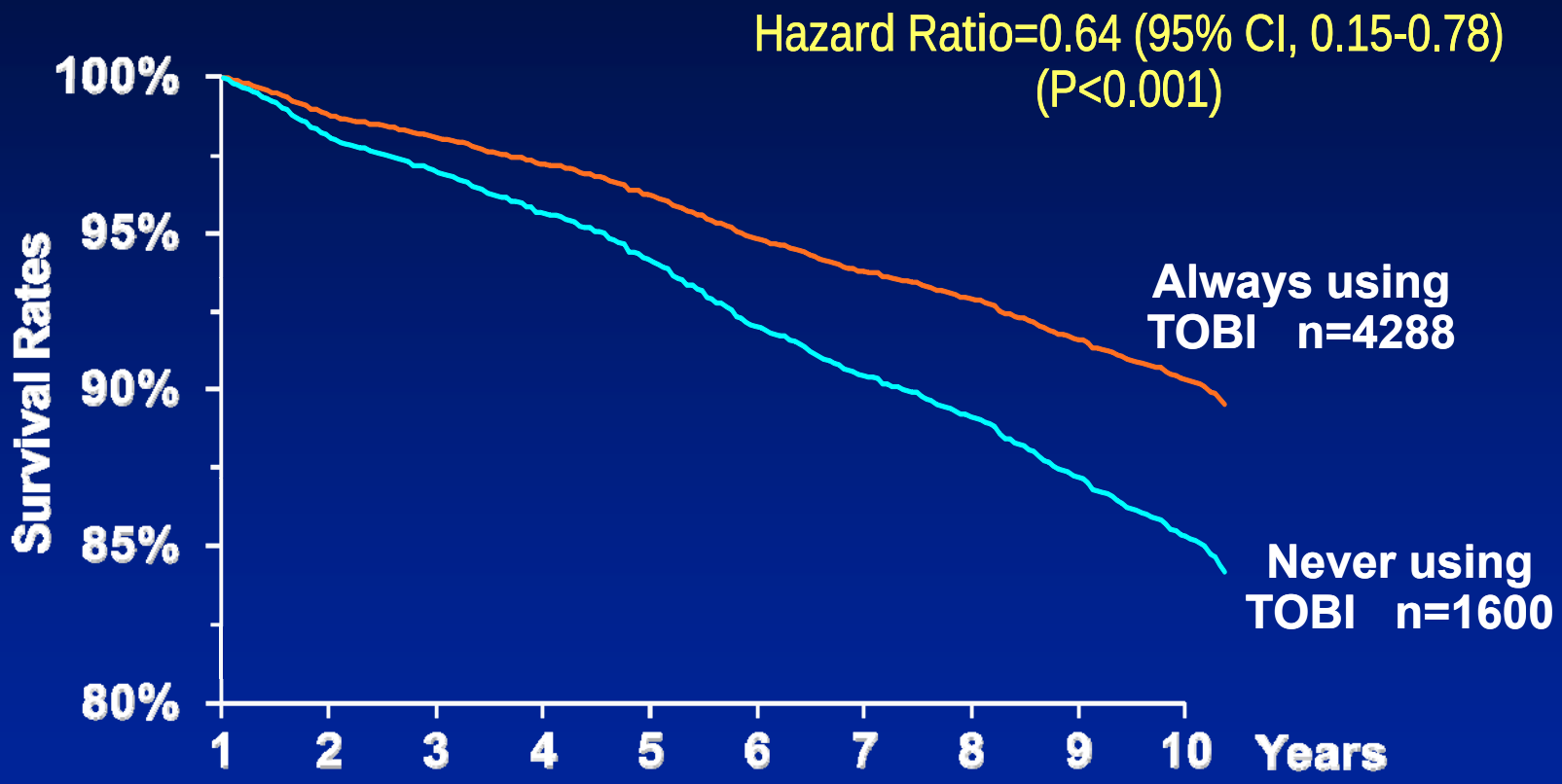
Logistic regression of probability of hospitalization of CF patients (N=804)			
Overall adherence with TOBI	**Utilization**	**OR***	**95% CI**
Low (≤2 cycles) (n=570)	71%	1.0	
Medium (>2 to <4 cycles) (n=180)	22%	0.94	0.62–1.41
High (≥4 cycles) (n=54)	6%	0.40	0.19–0.84

- High adherence reduces hospitalization by 60%[1]
- Poor adherence may limit the clinical benefits that inhaled tobramycin can offer

[1] Briesacher BA, et al. *BMC Pulmonary Medicine 2011, 11:5*.

* Adjusted for variables in the table and health plan type and geographic residence

Long-Term TOBI Use Results in a 36% Reduction in Mortality*



*Analysis of data from CFF registry from 1996-2008

Sawicki, et al. *Ped Pulm* (2011) 1-9

TIP – Important Treatment Option Addresses Unmet Needs for CF Patients

- Developed in response to requests from CF patients
- Reduces administration time
- Eliminates the need to disassemble, clean and sterilize aerosol equipment
- Improves portability, more discreet
- Comparable efficacy and safety to TOBI
- Reduces hospitalizations and other anti-pseudomonal antibiotic use

Dose Selection and Efficacy

Olga Santiago, MD

Clinical Science Unit Head

Novartis Pharmaceuticals Corporation

Overview of Presentation

- Dose selection and pharmacokinetics
- Phase 3 study designs and baseline characteristics
- Results of Studies C2301, C2302, C2303
  - Comparison across placebo controlled studies
  - Data across 3 cycles in Study C2303E1
- Summary and conclusions

Clinical Program Overview

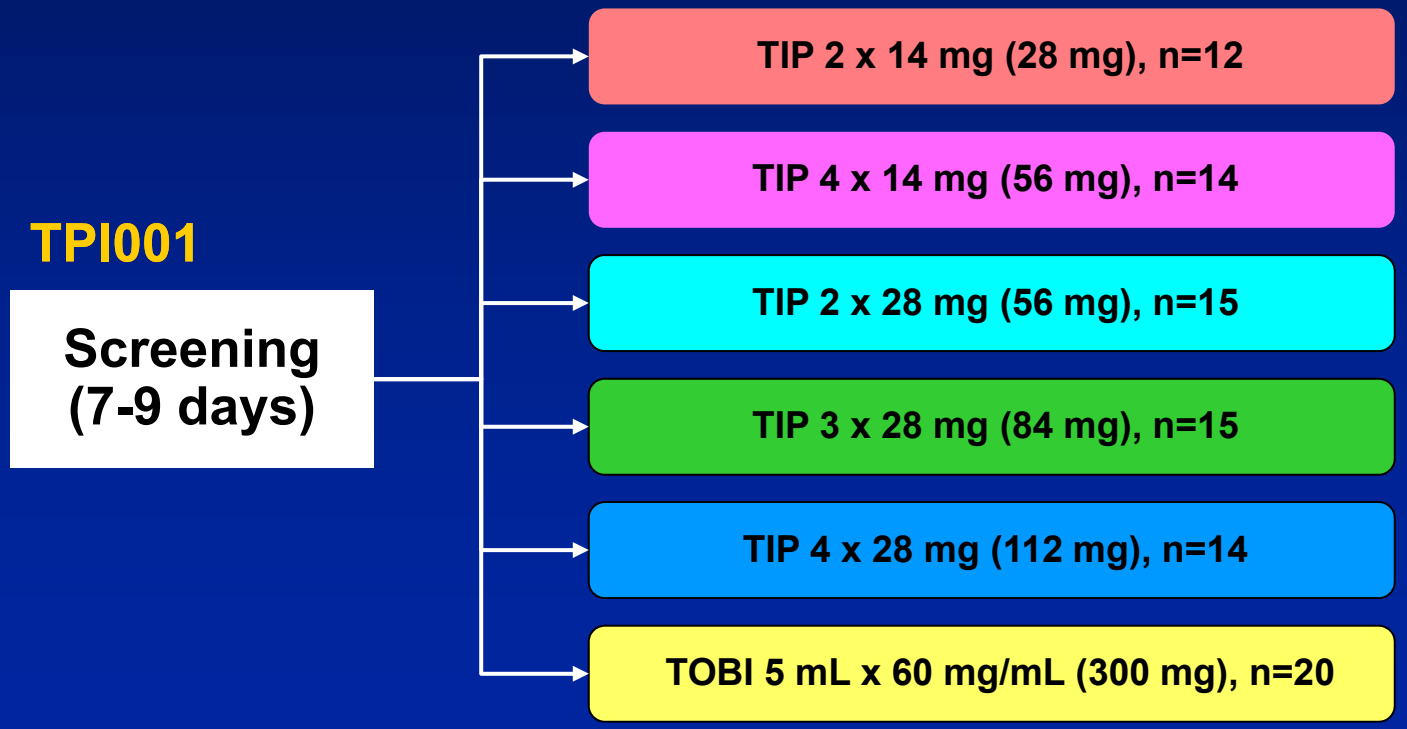
Large CF Clinical Program with More Than 650 Patients Included in Efficacy Analyses

Study	Objective	Patients Treated, n Age
TPI001	Dose selection	90 (≥6 years old)
C2301 Placebo-control	Efficacy and safety	95 (6-21 years)
C2302 Active-control	Safety and efficacy	517 (≥6 years old)
C2303 Placebo-control	Efficacy and safety	62 (6-21 years)
C2303E1 Extension	Safety and efficacy	55 (6-21 years)

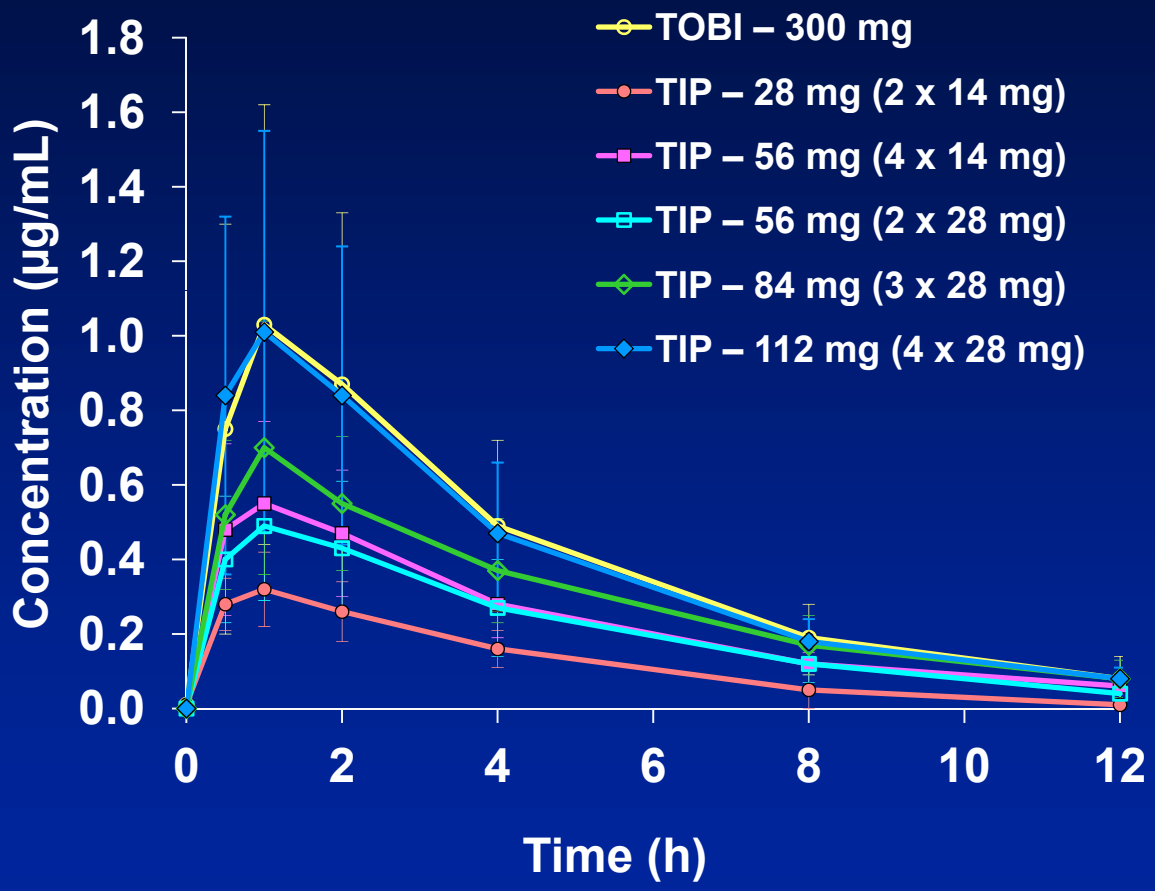
TPI001: Dose Selection and Pharmacokinetics

Wide Range of Doses Tested to Identify TIP Dose That Matches Pharmacokinetics of TOBI

- CF patients aged ≥6 years, FEV_1 ≥40% predicted
- No inhaled or intravenous aminoglycosides within 14 days prior to study drug administration



Selected TIP Dose (112 mg) Matches the Serum Pharmacokinetics of TOBI (300 mg)

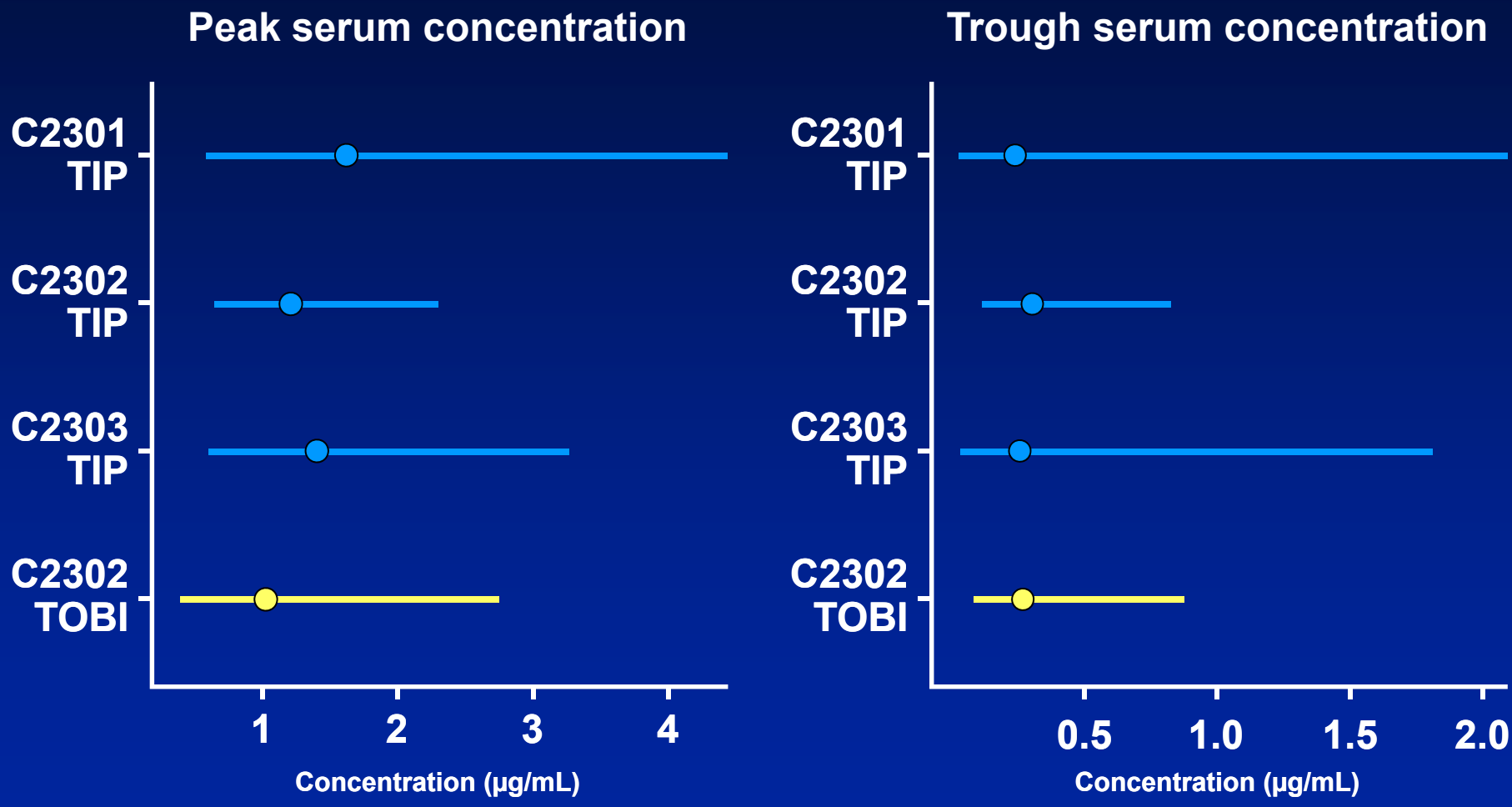


TPI001

- TIP 112 mg closest to TOBI 300 mg dose for PK exposure
- TIP pharmacokinetics are similar to TOBI despite very different delivery systems

Serum tobramycin only comes from the portion of the dose reaching the lung, as it is not absorbed in the gut

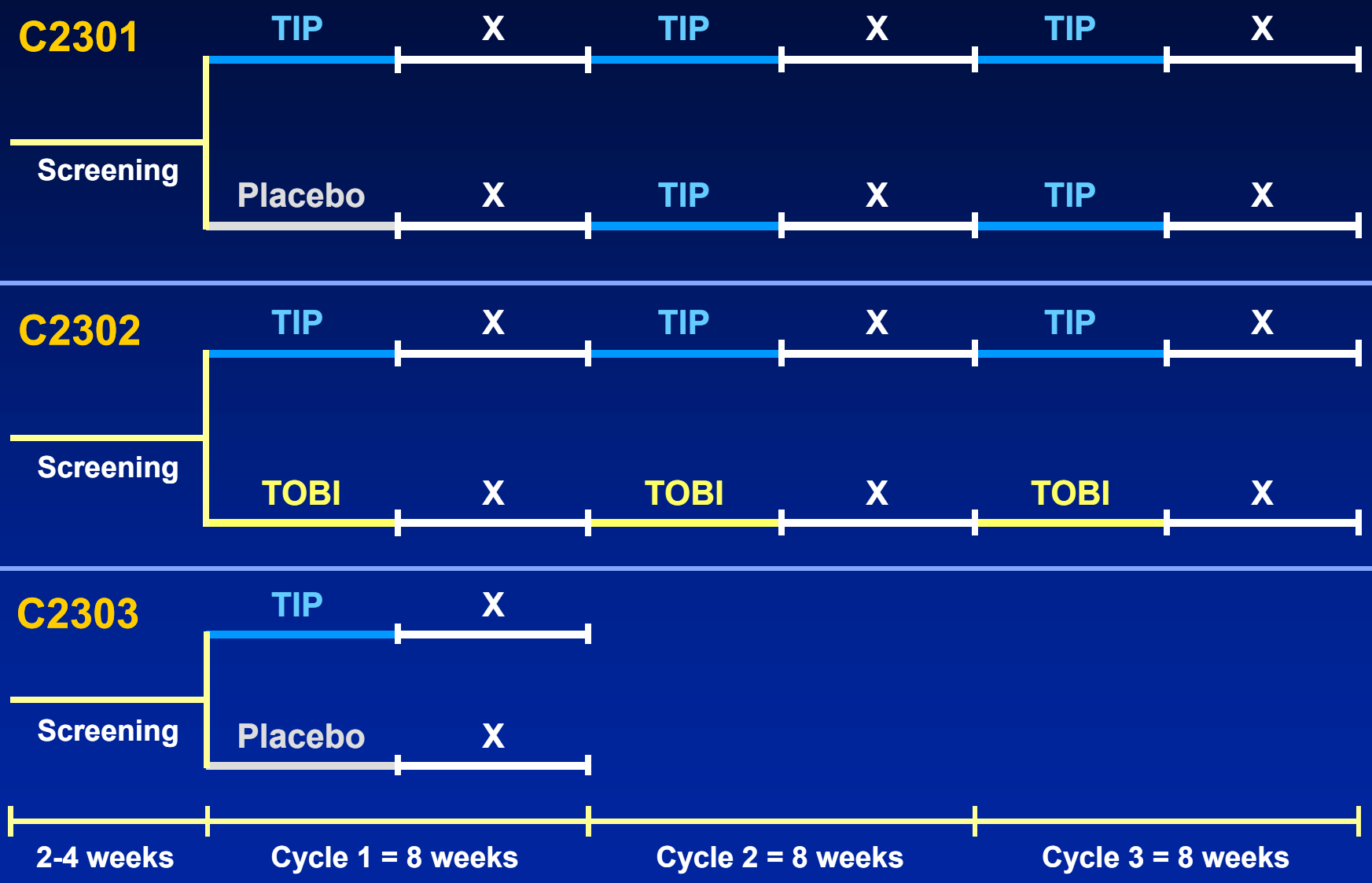
TIP Delivers Similar Amount of Tobramycin to the Serum as TOBI across Studies



Data presented as geometric mean (circle) and 90% confidence interval (line)
TOBI 300 mg; TIP 112 mg

Phase 3 Clinical Program

Overview of Phase 3 Study Designs



112 mg TIP BID; X = Standard Care during Off-TIP or Off-Placebo period

Main Phase 3 Entry Criteria Largely Consistent

INCLUSION

- Informed consent
- Diagnosis of CF
- *Pseudomonas aeruginosa* Infection confirmed
- Clinically stable
- On stable con-meds
- Aged
  - 6-21 yrs in C2301, C2303
  - ≥6 yrs in C2302

EXCLUSION

- History of *B. cepacia* complex within 2 years
- Hemoptysis >60 mL at any time within 30 days
- Serum creatinine >2 mg/dL, BUN >40 mg/dL or urinalysis with 2+ or greater proteinuria
- No inhaled anti-*Pa* antibiotics:
  - 4 months in C2301, C2303
  - 1 month in C2302 (normal off-cycle)
- No i.v. /oral anti-*Pa* antibiotics for 28 days

Key Phase 3 Endpoints to Support TIP's Efficacy and Other Clinical Benefits

Study	Key Endpoints
C2301	• Relative change in FEV_1 % predicted from Baseline to Day 28
	• Absolute change in FEV_1 % predicted (as post-hoc analysis)
	• Change in bacterial counts (CFUs)
	• New anti-*Pa* antibiotic use/hospitalizations for pulmonary exacerbations
C2302	• Safety
	• Relative change in FEV_1% predicted after 3 cycles
	• Change in bacterial counts (CFUs)
	• New anti-*Pa* antibiotic use/hospitalizations for pulmonary exacerbations
	• Administration time and TSQM
C2303	• Relative change in FEV_1% predicted from Baseline to Day 29
	• Absolute change in FEV_1 % predicted (pre-planned analysis)
	• Change in bacterial counts (CFUs)
	• New anti-*Pa* antibiotic use/hospitalizations for pulmonary exacerbations
	• CFQ-R
C2303E1	• Safety
	• Efficacy same as C2303, Relative & Absolute change in FEV_1% predicted

Phase 3 Trials: Patient Disposition

Stage	C2301		C2302 (Safety Trial)		C2303		C2303 E1
Recruited/ Screened	102		553		103		n.a.
Received study drug	TIP 46	Pbo 49	TIP 308	TOBI 209	TIP 32	Pbo 30	55
Completed	39 (85%)	40 (82%)	225 (73%)	171 (82%)	29 (91%)	30 (100%)	52 (95%)
Compliance (% of total dose)	91*	88.9*	90.3	94.3	97.8*	100*	97.4

* Cycle 1 only

Baseline Characteristics Comparable in C2301 and C2303, Older Patients in C2302

	C2301		C2302 (Safety Trial)		C2303	
	TIP (n=46)	Placebo (n=49)	TIP (n=308)	TOBI (n=209)	TIP (n=30)	Placebo (n=32)
Age (years), mean (SD)	13.4 (4.4)	13.2 (3.9)	25.9 (11.4)	25.2 (10.2)	12.9 (4.3)	12.9 (4.7)
Weight (Kg), mean (SD)	37.1 (14.7)	38.4 (12.5)	56.2 (15.6)	55.8 (14.6)	34.6 (13.6)	36.2 (15.2)
Height (cm), mean (SD)	146.1 (17.4)	147.7 (16.3)	163.5 (13.9)	164.1 (13.3)	143.5 (17.5)	145.5 (22.1)
FEV_1 % predicted, mean (SD)	54.7 (18.9)*	58.5 (20.0)*	52.9 (14.2)	52.8 (15.9)	59.1 (18.2)	59.3 (16.6)

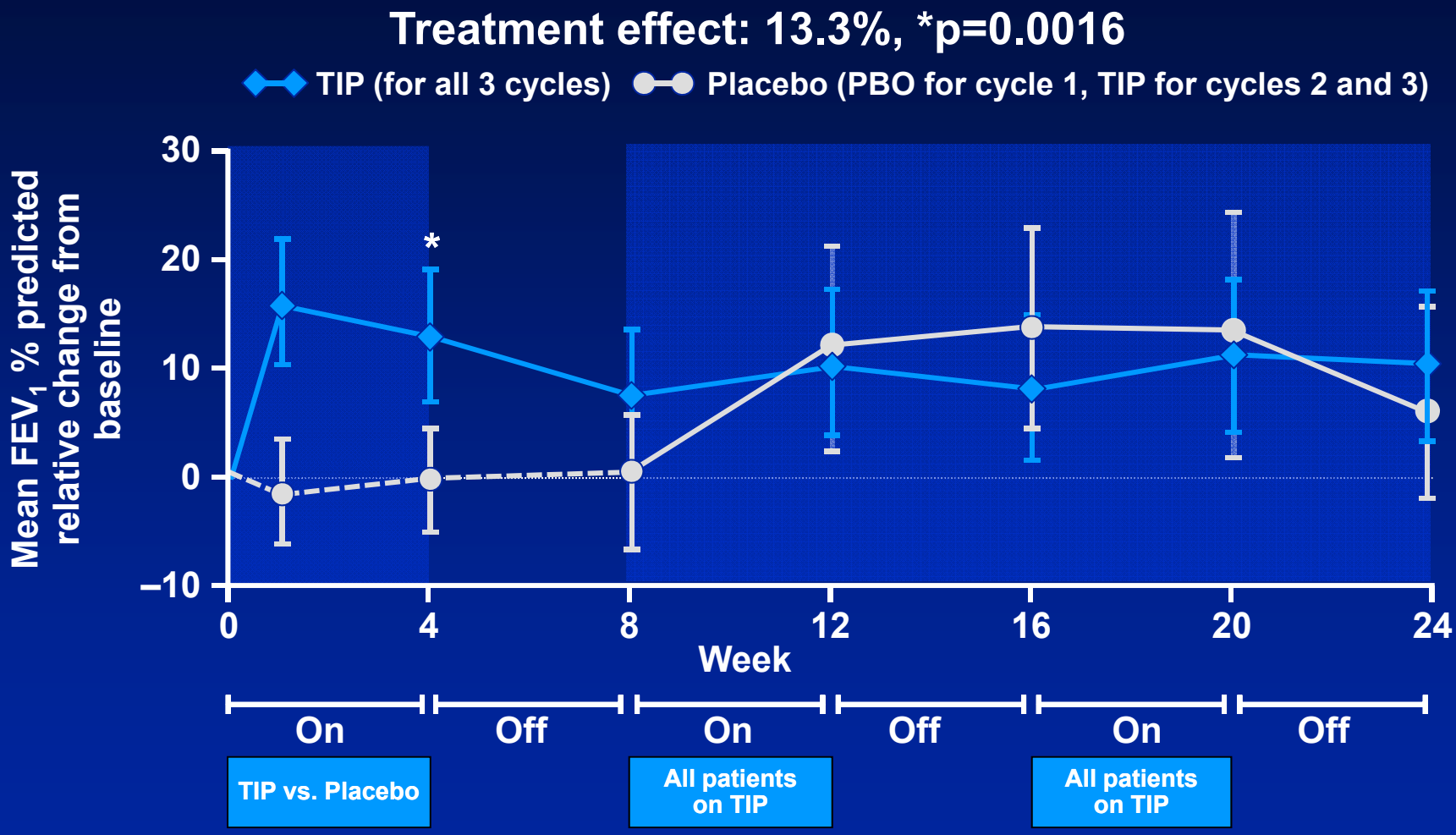
* Excluding patients from Latin American sites where spirometry data did not meet ATS/ERS criteria: TIP n=32, placebo n=37 in the Sensitivity Interim Analysis (SIA) all safety population

C2301:
Placebo-controlled Trial

C2301 Statistical Considerations

- Planned sample size N=140, assumes 11% effect size for relative change in FEV_1 % predicted
- Primary analysis based on Day 28 observed data, no imputation pre-specified
- Planned interim analysis N=80, conducted N=79
  - Pre-specified stopping rules for efficacy
- Interim analysis repeated after blinded external review of spirometry data quality
  - Sensitivity interim analysis N=61
- Independent DMC review recommended stopping study due to conclusive benefit vs. placebo

C2301 Primary: Statistically Significant Difference for FEV_1 vs. Placebo at Day 28



SIA population, N=61

FEV_1 = forced expiratory volume in one second

Konstan et al. *Ped Pulm* 2010

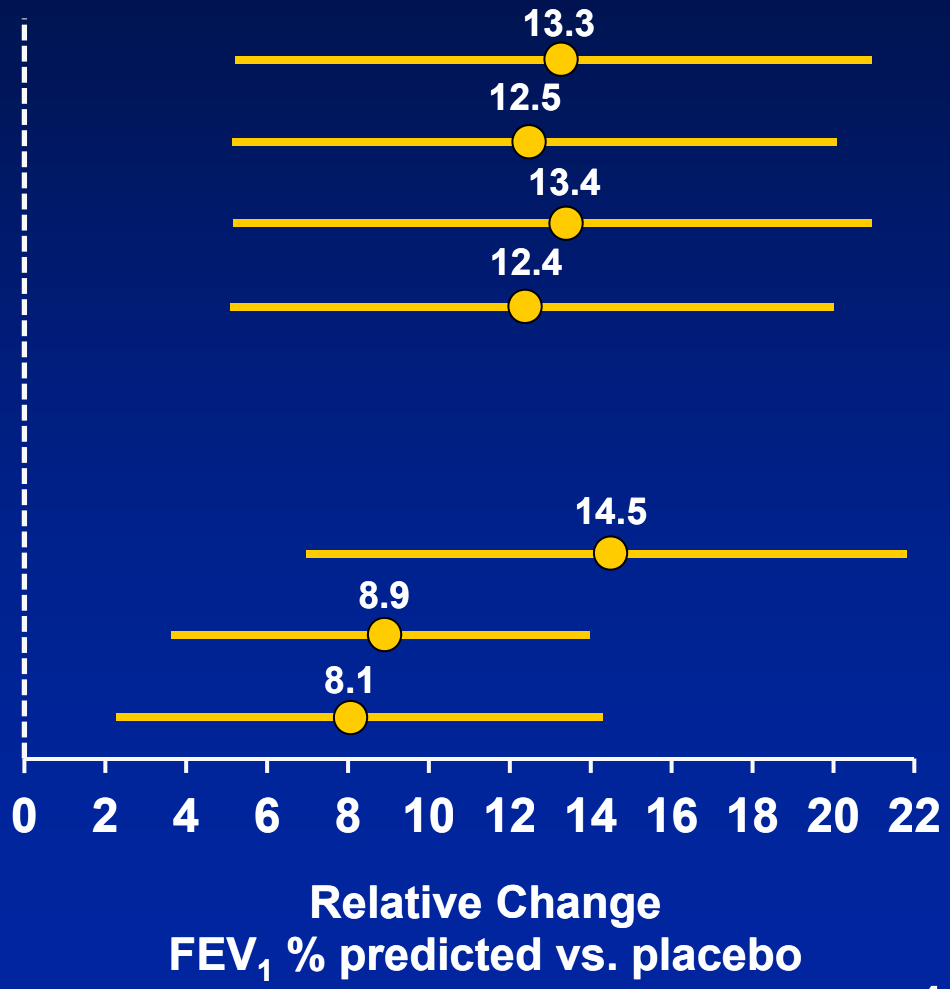
C2301: Consistent FEV_1 Treatment Effect across All Analyses Populations

Sensitivity Interim Analysis (N=61)

- Observed data (n=58)
- ITT with BOCF (missing data with zero)
- Multiple imputation
- Least favorable mean imputation (imputing with placebo mean, *consistent with FDA Reviewer*)

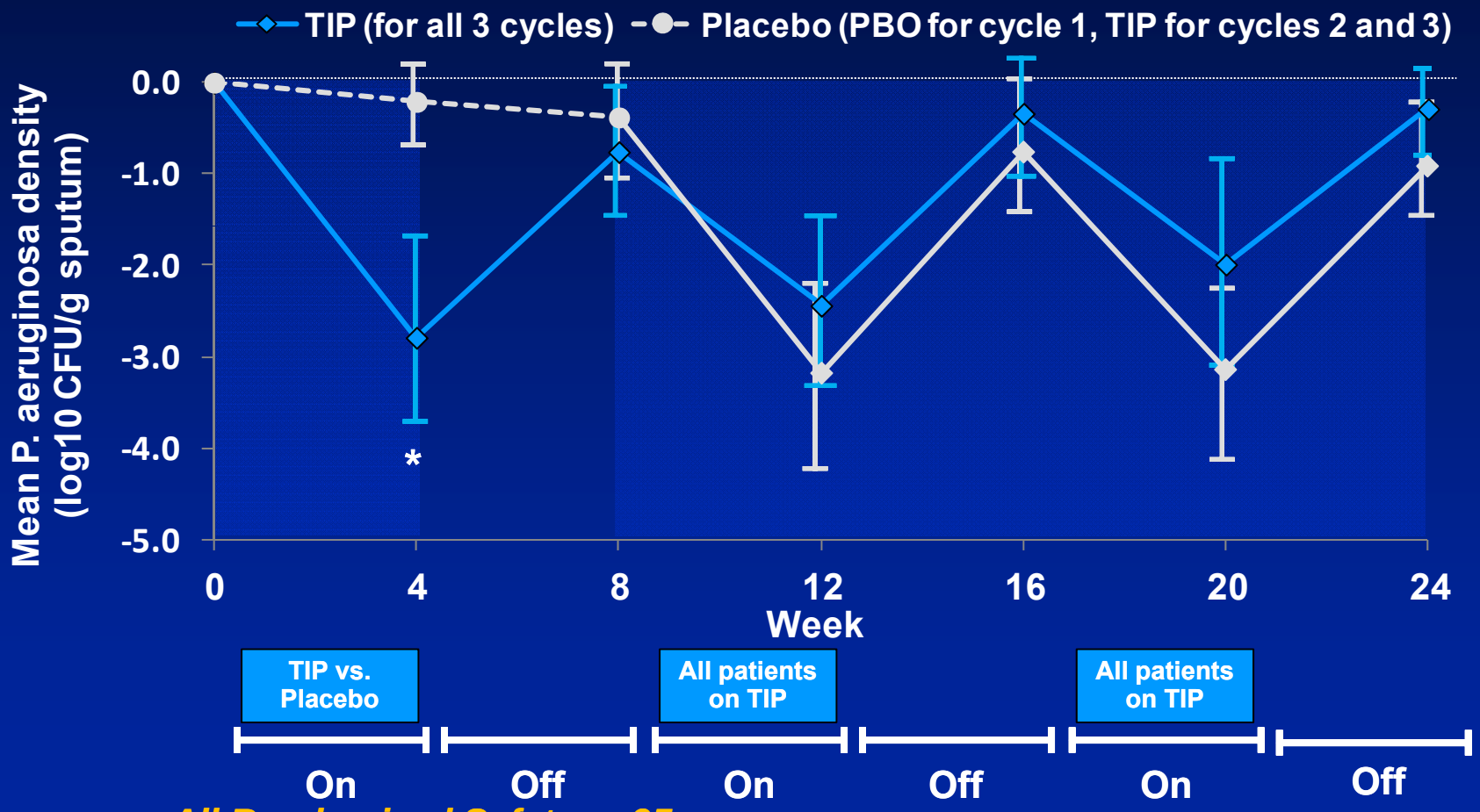
All randomized safety (N=95)

- Observed data (n=62)
- ITT with BOCF (missing data with zero)
- *FDA Reviewer*



C2301: Effective Suppression of *P. aeruginosa* at Day 28

CFU difference vs. placebo: -2.7 $\log_{10}$, *p<0.001



All Randomized Safety n=95

CFU = colony forming unit

Konstan et al. *Ped Pulm* 2010

C2301: Other Clinical Endpoints

Endpoint	TIP	Placebo
Rate of new anti-*Pa* antibiotic use	13.0% (6 patients)	20.4%* (10 patients)
Duration of new anti-*Pa* antibiotic use (mean days)	13.3 days	18.2 days
Hospitalization for pulmonary exacerbation	0 (2 patients**)	12.2% (6 patients)

All Randomized Safety, N=95

* Analysis of new anti-*Pa* antibiotic use re-run with same antibiotic list as C2302/C2303, excludes azithromycin; FDA BB uses C2301 CSR: 9 patients (18.4%)

** FDA BB uses 2 patients (4.4%) with hospitalization verbatim rather than investigator assessment: CF pulmonary exacerbation, CF exacerbation (FDA BB)

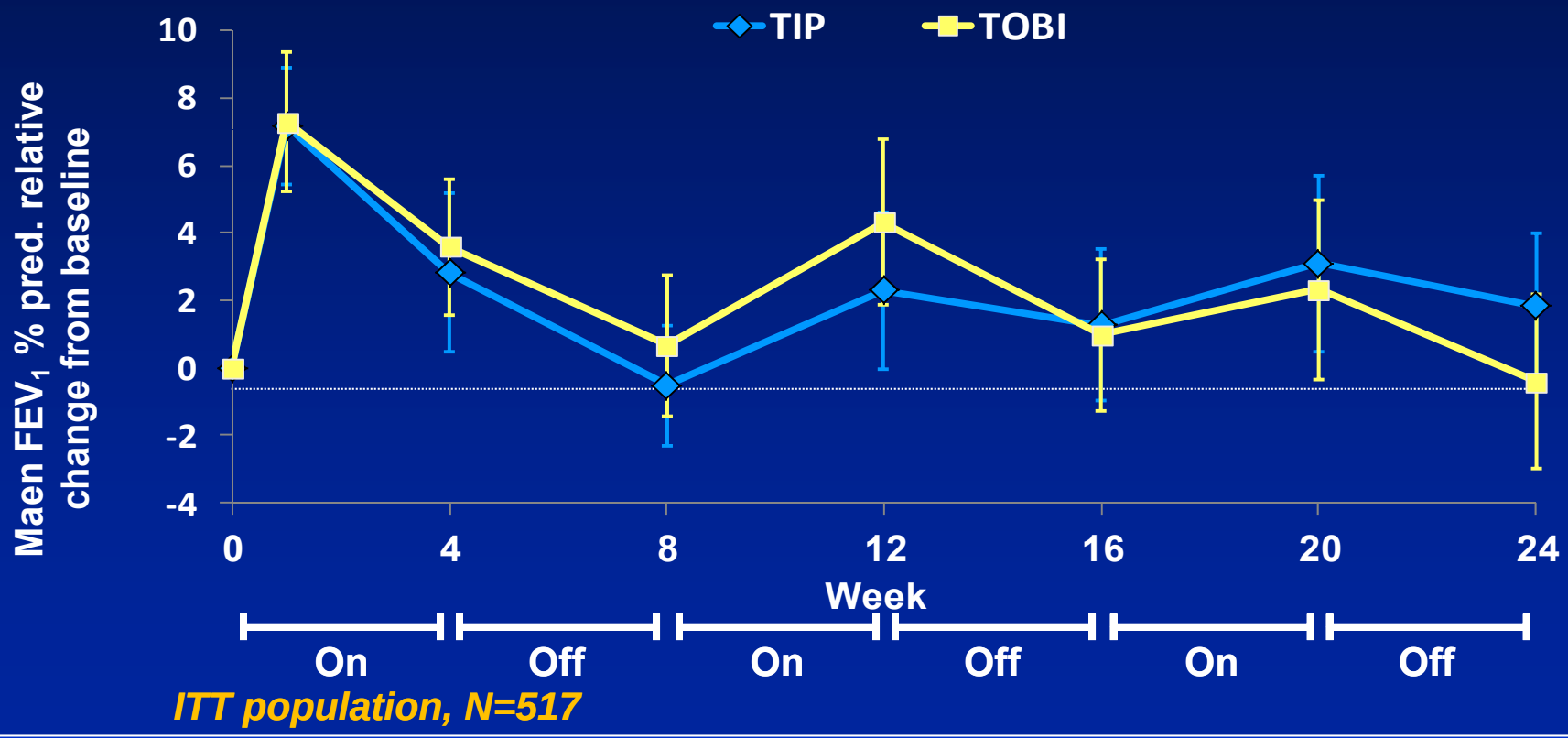
C2302:
Active Controlled Trial
(TIP vs. TOBI)

C2302 Statistical Considerations

- Planned sample size N=500, 3:2 randomization
  - 300 TIP patients provides 95% chance of observing at least 1 adverse event with a true incidence rate of 1%, 99.8% for 2%
- Main efficacy analysis based on FEV_1 Week 20 observed data, no imputation pre-specified
- 96% power for non-inferiority, 6% margin
  - Assumes TIP – TOBI difference of -1%, one-sided α=0.15 and SD 20%; α=0.025 also evaluated

C2302: TIP vs. TOBI for Change in Relative FEV_1 % Pred. at Week 20 and across 3 Cycles

Week 20	TIP, N=308	TOBI, N=209	Difference (SE)	95% CI; 2-sided
N (completers)	227	171		
LS Mean	5.8	4.7	1.1 (1.75)	(-2.3, 4.49)

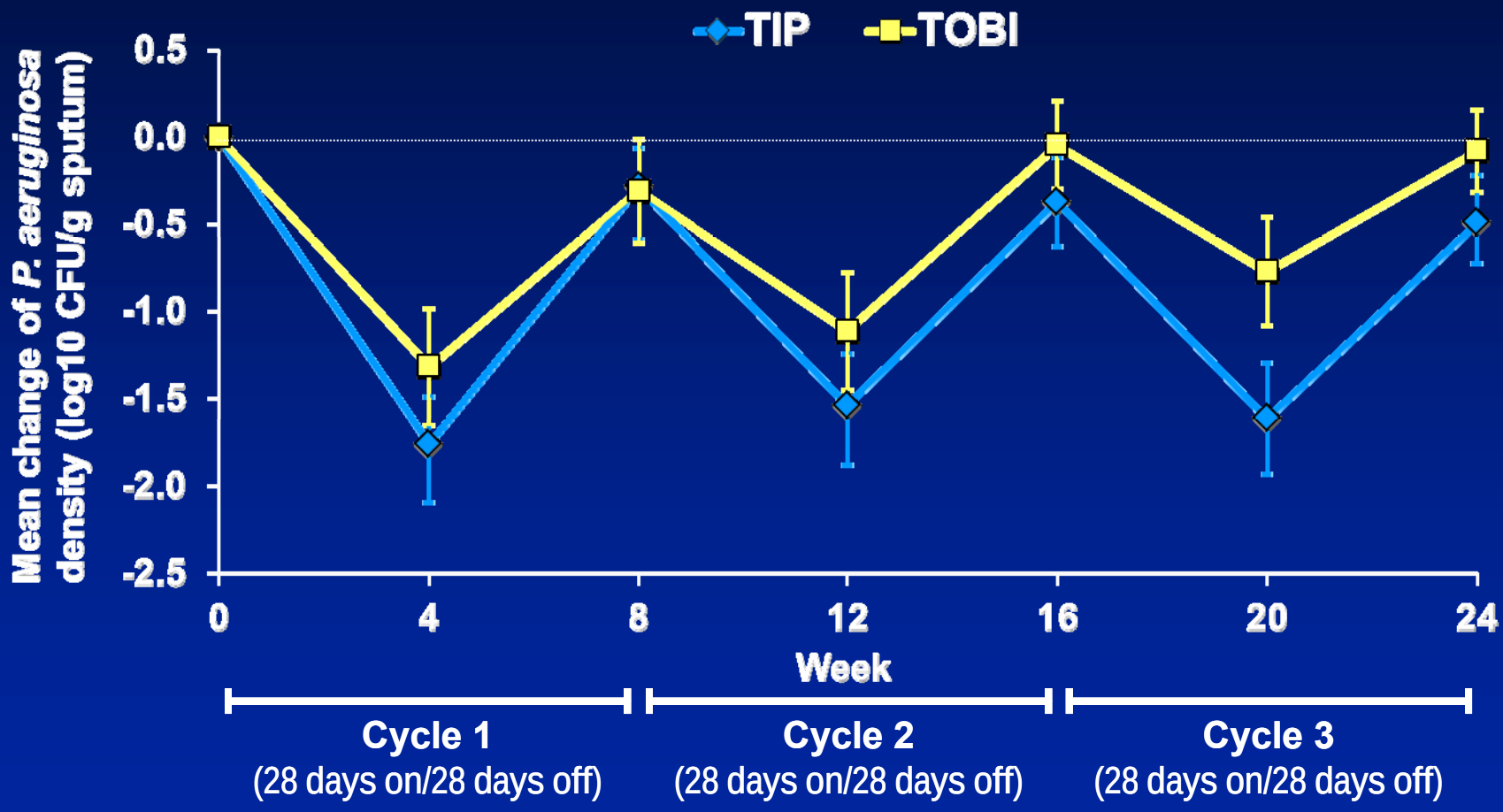


ITT population, N=517

Repeated measure across 3 cycles: Treatment difference -0.09, p=0.93, CI (-2.12, 1.94)

Konstan MW, et al. *J Cyst Fibros* 2011;10:54–61

C2302: TIP Showed Consistent, Numerically Lower Sputum *P. aeruginosa* Density



ITT population, N=517

Konstan MW, et al. *J Cyst Fibros* 2011;10:54–61

C2302: Other Clinical Endpoints

Endpoint	TIP	TOBI
Rate of new anti-*Pa* antibiotic use	64.9%	54.5%
i.v.	34.7%	33.0%
oral	54.9%	39.7%
Duration of new anti-*Pa* antibiotic use (mean days)	30.9	33.4
Hospitalization for pulmonary exacerbation	24.4%	22.0%
Days in hospital	15.6	15.3

ITT population, N=517

C2302: TIP is Quicker, More Convenient to Use

Administration Time

TIP N=308 min, LS Mean	TOBI N=209 min, LS Mean	LS Mean Difference (SE)	p-value
5.6	19.7	-14.1 (0.3)	<0.0001

TSQM

	Average Treatment Over All Visits			
	TIP N=308	TOBI N=209	LS Mean Difference (SE)	p-value
Effectiveness	74.8	65.4	9.4 (1.5)	<0.0001
Impact of side effects	92.1	92.6	- 0.5 (1.2)	0.6833
Convenience	82.7	58.4	24.4 (1.6)	<0.0001
Global satisfaction	76.2	71.0	5.20 (1.7)	0.0018

ITT population, N=517

TSQM = Treatment Satisfaction Questionnaire for Medication – modified

Improved Satisfaction with Medication Is Associated with Improved Adherence

- Strong link between satisfaction and compliance[1]
  - 20 studies show positive association between treatment satisfaction and adherence or persistence
  - 16 studies show statistically significant link between satisfaction and compliance or persistence
- Association between key domains of patient satisfaction and compliance shown in C2302 TSQM validation study[2]

Sources: [1]Barbosa et al, 2012; [2]Regnault et al, 2012

C2303:
Placebo-controlled Trial

C2303: Statistical Considerations

- Planned sample size N=100, assumes 11% effect size for relative change in FEV_1 % pred.
- Imputation with BOCF for missing data in ITT
  - Imbalance of excluded spirometry data: 4 TIP, 1 placebo
  - Mis-dispensed treatment: 2 assigned TIP received placebo

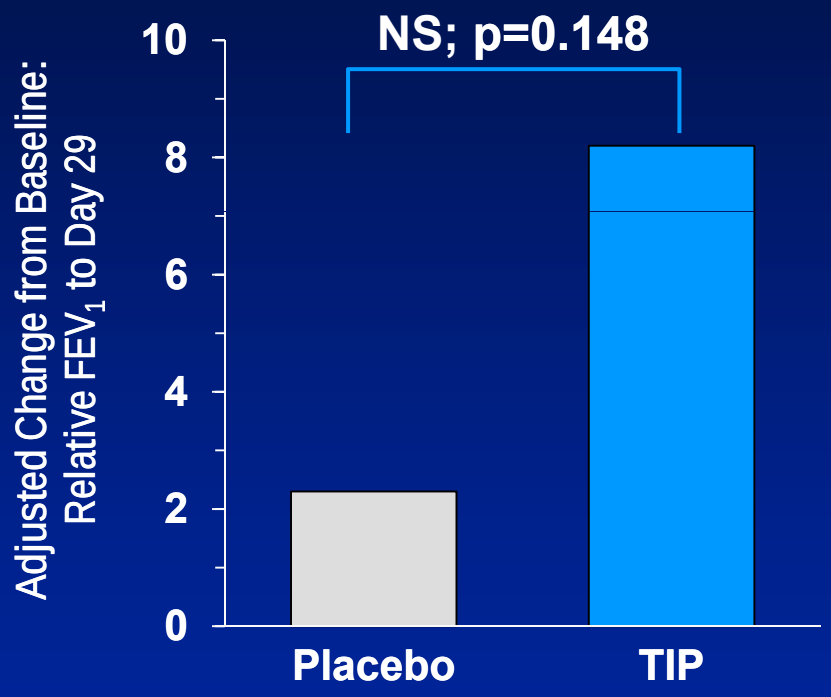
BOCF = Baseline Observation Carried Forward; ITT = Intent-to-Treat

C2303: Clinical Challenge

- Placebo control and requirement for “TOBI naïve” patients impacted trial feasibility
  - Recruitment only feasible in countries with no or very limited access to TOBI
  - Clinical and ethical standards evolved since C2301; conducted outside US/Western Europe
  - 62 of 100 patients enrolled

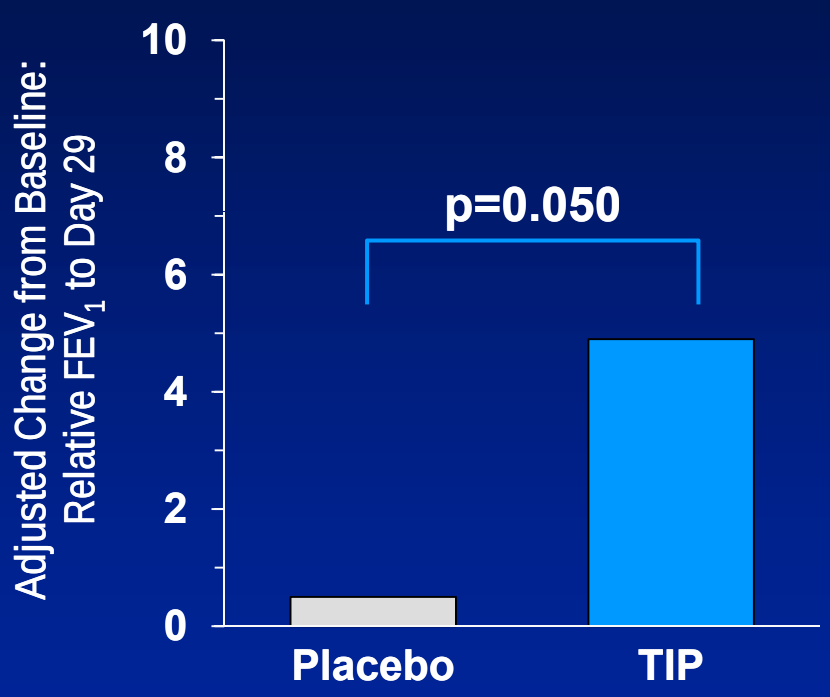
C2303 Primary: Favorable Trends in Relative and Absolute FEV_1 % Predicted

Relative Change



From Baseline to Day 29:
Treatment Difference 5.9
95% CI (-2.2,14.0)

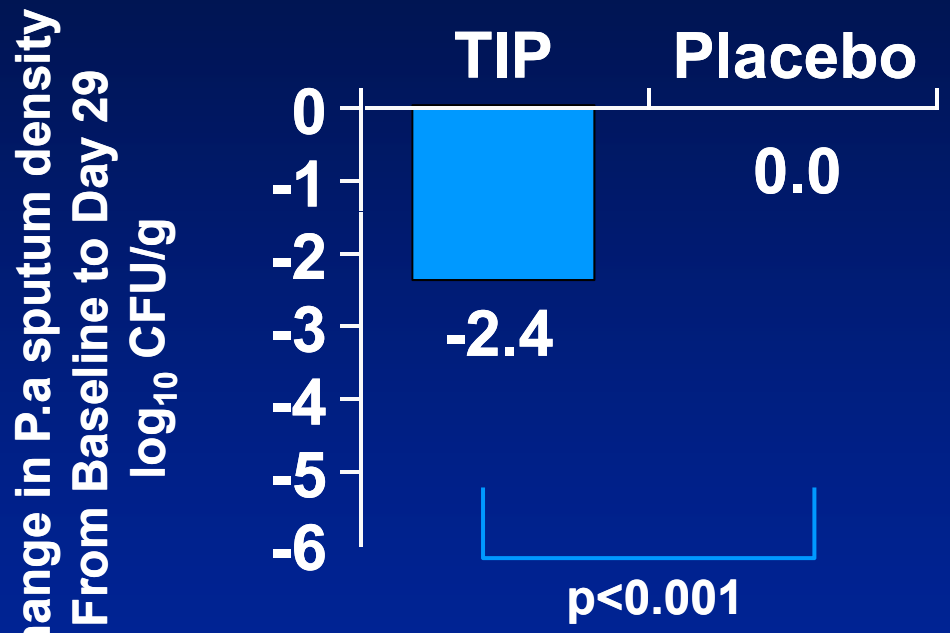
Absolute Change



From Baseline to Day 29:
Treatment Difference 4.4
95% CI (0.0,8.8)

ITT pop. with BOCF, N=59

C2303: Effective Suppression of *P. aeruginosa* TIP vs. Placebo



From Baseline to Day 29:
Treatment Difference -2.4
95% CI (-3.18, -1.54)

Observed Data

C2303: Other Clinical Endpoints

Endpoint	TIP	Placebo
Rate of new anti-*Pa* antibiotic use*	6.7%** (2 patients)	12.5% (4 patients)
Duration of new anti-*Pa* antibiotic use	8.3 days	13.0 days
Hospitalization for pulmonary exacerbation	0	3.3% (1 patient)

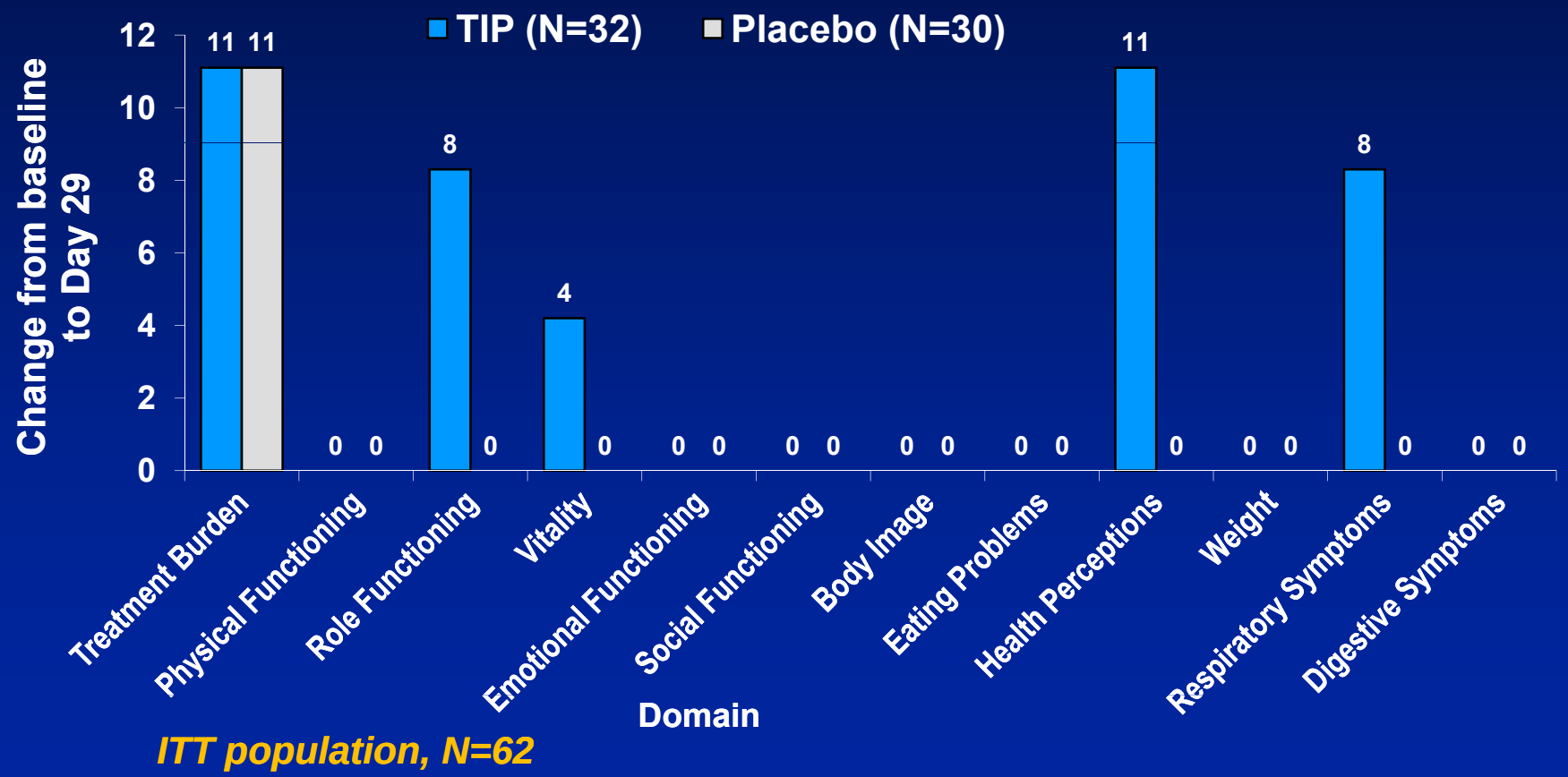
ITT population, N=62

* Assessed for treatment received

** Includes one patient who received routine prophylaxis (i.e. was not treated for an exacerbation)

C2303: Patients Reported Improved Health-related QoL vs. Placebo

- CFQ-R median changes indicated improvements in relevant domains



ITT population, N=62

CFQ-R: Revised Cystic Fibrosis Quality of Life Questionnaire

Comparison of Placebo-controlled Trials C2301, C2303

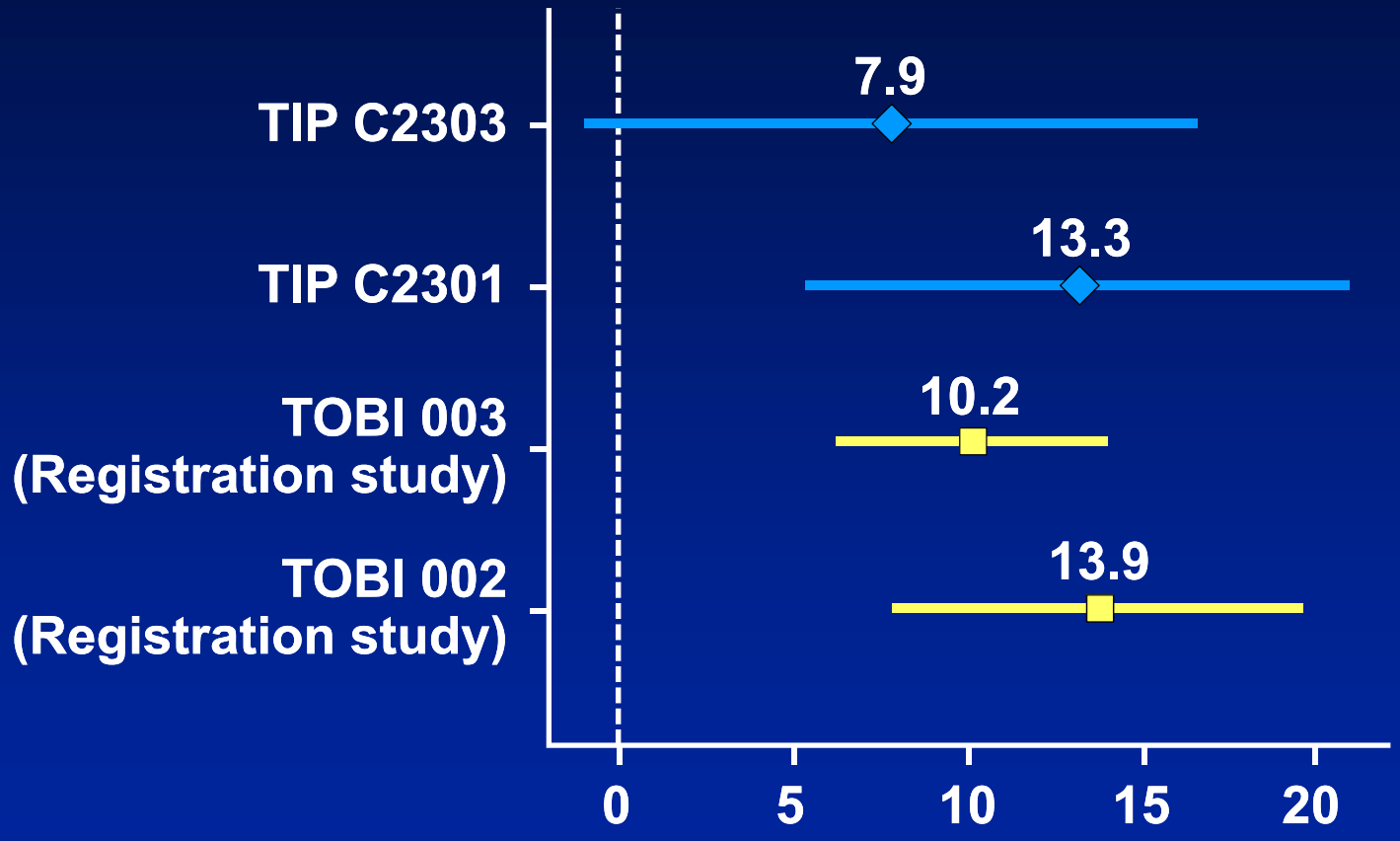
C2301 and C2303: FEV_1 and CFU Responses Are Comparable after 28 Days of Treatment

	C2301		C2303	
	TIP	Placebo	TIP	Placebo
LS mean FEV_1 % predicted relative change (observed population), (%)	13.97	0.68	10.3	2.4
LS mean FEV_1 % predicted absolute change (observed population), (%)	6.38	–0.52	6.1	0.5
LS Mean log_{10} CFU change (observed population)	–2.86	–0.16	–2.31	–0.01
New anti-pseudomonal antibiotic use*, n (%)	6 (13.0)	10 (20.4)	2 (6.7)	4 (12.5)
Hospitalizations, n (%)	0** (0.0)	6 (12.2)	0 (0.0)	1 (3.3)

* Assessed for treatment received

** FDA BB uses 2 patients (4.4%) with hospitalization verbatim rather than investigator assessment: CF pulm. exacerbation, CF exacerbation (FDA BB)

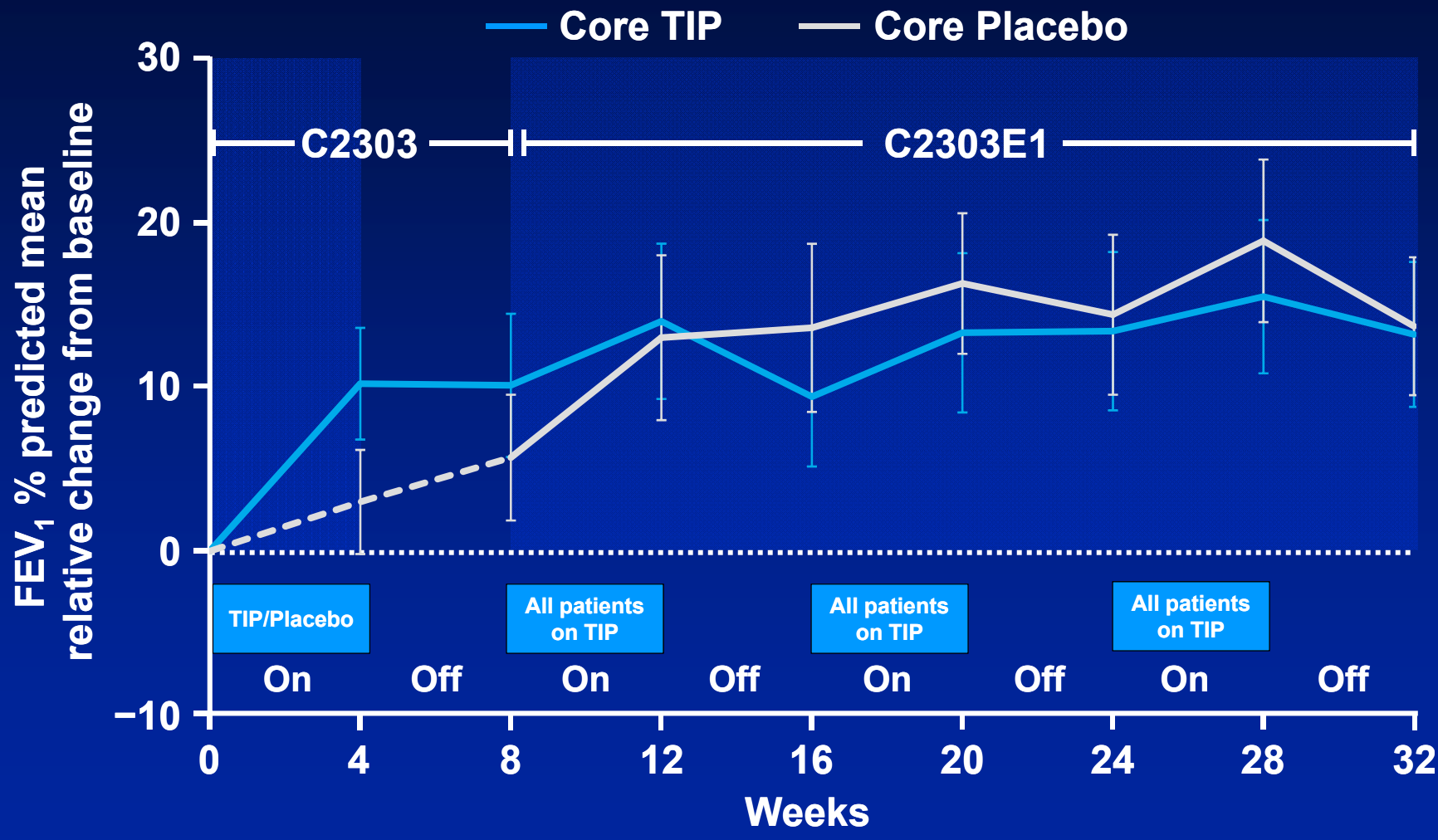
Overlapping Range of Relative FEV_1 Treatment Effect across TIP and TOBI Programs



Observed data at Day 29; difference vs. placebo

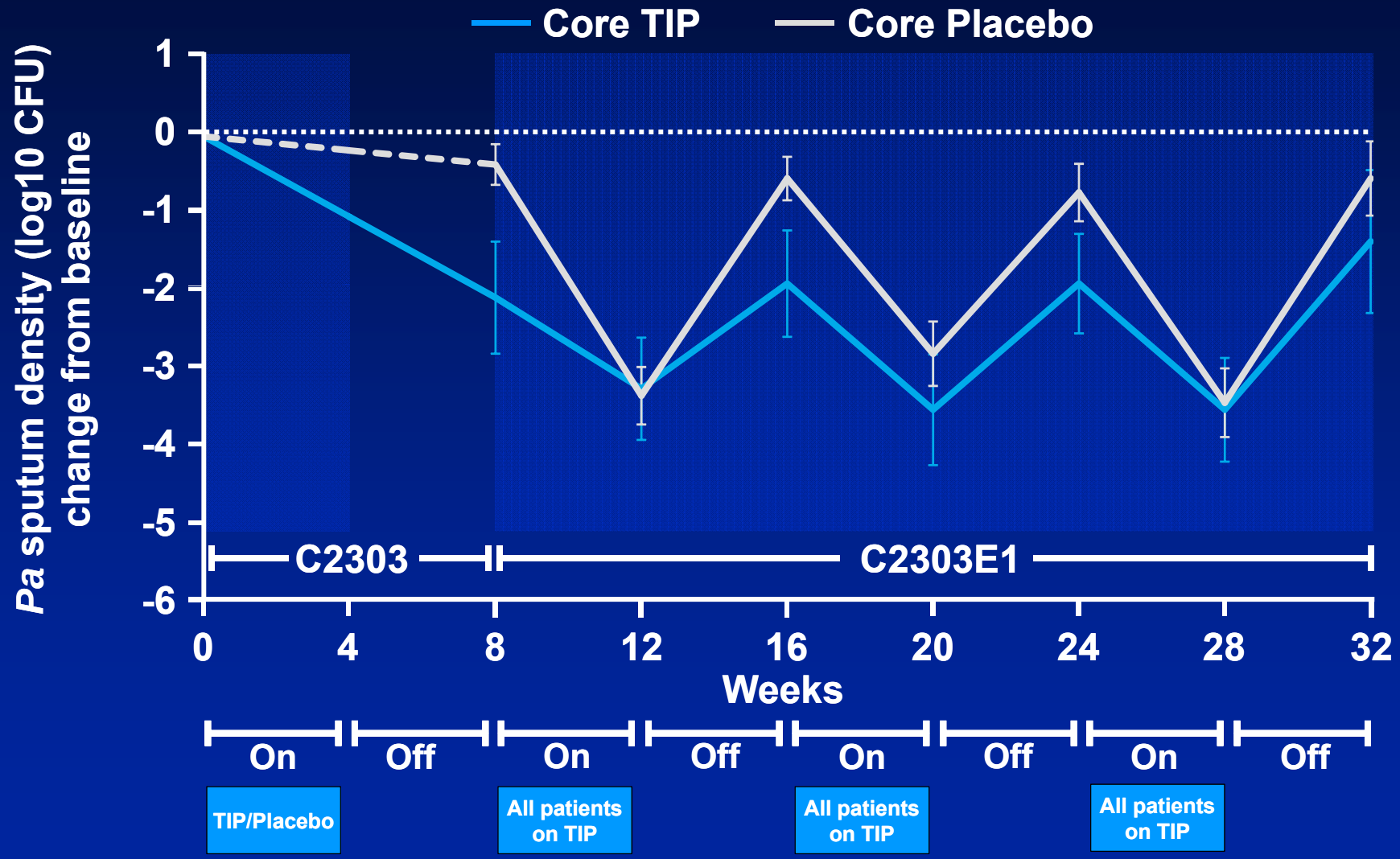
C2303E1:
Extension Study

C2303E1: Improvement in Placebo, Then Relative FEV_1 Effect Sustained



Group originally receiving placebo show continued strong improvement in E1

C2303 E1: Sustained Suppression of *P. aeruginosa*



Model: response (% change) = treatment + screening FEV_1 % predicted (<50 and ≥50) + age (<13 and ≥13) + error
Pa sputum density refers to overall density, defined as the sum of biotypes (mucoid, dry and small colony variant)

Efficacy Summary and Conclusions

- Comparable systemic exposure
  - TIP 112 mg and TOBI 300 mg
- Lung function improved vs. placebo, similar to TOBI
  - Relative change in FEV_1 % pred., pre-specified primary analysis
    - C2301: treatment effect 13.3%, p=0.0016
    - C2302: TIP & TOBI similar, LS mean Δ vs. TOBI 1.1%
    - C2303: treatment effect 5.9%, p=0.148
  - Absolute change in FEV_1 % pred., observed data
    - C2301: treatment effect 6.9%, p=0.0033
    - C2303: treatment effect 5.6%, p=0.025
- Sustained FEV_1 effect across 3 extension cycles with 95% completion rate

Totality of Evidence Confirms TIP Efficacy

- Consistent and sustained FEV_1 response across studies
- *P. aeruginosa* density reduced in 3 pivotal studies
- Use of new anti-pseudomonal antibiotics and hospitalizations less common with TIP than placebo
- Hospitalization rates similar for TIP and TOBI
- TIP 112 mg provides efficacy similar to TOBI 300 mg with
  - Ease of use; shorter administration time
  - Greater convenience and global satisfaction
  - Lower treatment burden for CF patients

Safety and Benefit Risk

Linda Armstrong, MD

Therapeutic Area Safety Lead

Novartis Pharmaceuticals Corporation

Safety Agenda

- Review of TOBI® (inhalation solution) post-marketing experience
- Tobramycin Inhalation Powder (TIP) development program
- Overview of adverse events
- Areas of special interest
  - Local adverse reactions (cough, airway reactivity)
  - Systemic adverse reactions (ototoxicity, renal effects)
  - Microbiology (changes in MIC, treatment emergent organisms)
- Post-approval experience of TIP

TOBI® Post-marketing Experience

- 197,218 patient-treatment years since approval in 43 countries
- In post-marketing experience, spontaneous reports are consistent with known side effect profile
- No recent changes to prescribing information

TIP and TOBI Have Comparable Pharmacokinetic Profiles

- Systemic levels with TIP are well-below the known toxicity levels for nephrotoxicity (2 µg/mL trough)

	Geometric mean (90% CI)		
Study	**C_{trough} (µg/mL)**	**C_{max} (µg/mL)**	**$AUC_{0-\infty}$ (µg·hr/mL)**
TPI001 – TOBI	N/A	0.92 (0.40, 2.10)	4.8 (2.2, 10.4)
TPI001 – TIP	N/A	0.90 (0.38, 2.11)	4.7 (2.5, 9.0)
Phase 3 studies – end of dosing cycle			
C2302 – TOBI	0.27 (0.08, 0.87)	1.02 (0.38, 2.73)	N/A
C2302 – TIP	0.31 (0.11, 0.82)	1.21 (0.64, 2.28)	N/A
C2301 – TIP	0.24 (0.03, 2.08)	1.61 (0.59, 4.41)	N/A
C2303 – TIP	0.26 (0.04, 1.81)	1.40 (0.60, 3.25)	N/A

AUC = area under the curve, C_{max} = maximum concentration, C_{trough} = trough concentration

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TIP Clinical Program

Phase 3 Studies

- **Primary Safety Population**
  - C2302 (N=517)
- **Placebo-controlled Studies**
  - C2301 (N=95)
  - C2303 (N=62)

Exposure in TIP Phase 3 Program

Patients received TIP in 28 day on / 28 day off cycles

Days on TIP	C2302	C2301	C2303*	Total
>1 dose	308	87	30	425
>28 days	278	83	25	386
>56 days	249	78	0	327
>84 days**	218	36	0	254

* 55 patients have received TIP for an additional 3 cycles in C2303E1

** 24 weeks in study

Baseline Demographics were Comparable between C2301 and C2303; Older Patients Were Randomized in C2302

	C2301		C2302		C2303 (Safety Population)	
Mean values	TIP N=46	Placebo N=49	TIP N=308	TOBI N=209	TIP N=30	Placebo N=32
Age (years)	13	13	26	25	13	13
Weight (kg)	37	38	56	56	35	36
Height (cm)	146	148	164	164	144	146
FEV_1 % predicted	55*	59*	53	53	59‡	59‡

* Excluding patients from Latin American sites with any potential spirometer quality concerns (TIP n=32, placebo n=37); ‡TIP n=31, placebo n=28

Common Background Medications Associated with Systemic Toxicities

	C2302		C2301		C2303	
Drug class	TIP	TOBI	TIP	Pbo	TIP	Pbo
Enzyme Prep	88%	90%	74%	86%	70%	91%
Dornase alfa	71%	71%	59%	74%	73%	78%
Macrolides	47%	45%	7%	12%	17%	31%
Parenteral Aminoglycosides	33%	32%	9%	8%	3%	3%
Corticosteroids	31%	25%	15%	14%	10%	13%
NSAIDs	23%	23%	7%	8%	0%	0%

Pbo: placebo

Safety Agenda

- Review of TOBI® (inhalation solution) post-marketing experience
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- Areas of special interest
  - Local adverse reactions (cough, airway reactivity)
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Common AEs

C2302: Primary safety population ≥10%

Preferred term	TIP (OL) N=308 n (%)	TOBI (OL) N=209 n (%)
Subjects with AE(s)	278 (90)	176 (84)
Cough	149 (48)	65 (31)
Lung disorder	104 (34)	63 (30)
Sputum increased	53 (17)	35 (17)
Dyspnea	48 (16)	26 (12)
Pyrexia	48 (16)	26 (12)
Oropharyngeal pain	43 (14)	22 (11)
Dysphonia	42 (14)	8 (4)
Hemoptysis	40 (13)	26 (12)
Headache	35 (11)	25 (12)
Nausea	23 (8)	20 (10)

OL: Open-label

Common AEs

C2301 and C2303: Placebo-controlled studies ≥5%

		TIP N=76	Placebo N=81
Total AEs n (%)		31 (41)	48 (59)
AEs classified as Severe n (% of all events)		1 (1)	1 (1)
Cough	Total AEs	9 (12)	13 (16)
	Severe AEs	0	0
Lung disorder (cystic fibrosis exacerbation)	Total AEs	5 (7)	6 (7)
	Severe AEs	0	1 (1)
Dysgeusia (Bad taste)	Total AEs	4 (5)	1 (1)
	Severe AEs	1 (1)	0
Oropharyngeal pain (Sore throat)	Total AEs	5 (7)	0
	Severe AEs	0	0

Adverse Events Leading to Discontinuation (≥3 Patients in Total)

C2302: Primary safety population

Preferred term	TIP (OL) N=308 n (%)	TOBI (OL) N=209 n (%)
Patients discontinued due to AE	43 (14)	17 (8)
Cough	12 (4)	2 (1)
Dyspnoea	8 (3)	4 (2)
Lung disorder	7 (2)	6 (3)
Chest discomfort	5 (2)	0
Bronchospasm	3 (1)	0
Dysphonia	3 (1)	0
Musculoskeletal chest pain	2 (1)	1 (1)
Hemoptysis	2 (1)	1 (1)
Productive cough	1 (0.3)	2 (1)
Pulmonary function tests decreased	1 (0.3)	4 (2)

OL: Open-label

Adverse Events Leading to Discontinuation

C2301 and C2303: Placebo-controlled studies

Study C2301	TIP N=46	Placebo N=49
Pulmonary Exacerbation	0	1 (2)

Study C2303	TIP N=30	Placebo N=32
Pulmonary Hemorrhage	1 (3)	0
Bronchitis	0	1 (3)

Completion Rate across Studies

Study	Treatment arm	Completion rate n (%)
C2301	Placebo	40 (82)
	TIP	39 (85)
C2302	TOBI	171 (82)
	TIP	225 (73)
C2303	Placebo	30 (100)
	TIP	29 (91)
C2303E1	TIP	52 (95)

Most Common Serious Adverse Events (SAE) by SOC (≥3 Patients)

C2302: Primary safety population

	TIP N=308	TOBI N=209
Total SAEs n (%)	**85 (28)**	**61 (29)**
Respiratory, thoracic, and mediastinal	68 (22)	46 (22)
Infection and infestation	22 (7)	14 (7)
Investigations (including FEV_1 decrease)	6 (2)	7 (3)
Gastrointestinal disorders	5 (2)	6 (3)
General disorders	5 (2)	2 (1)
Metabolism and nutrition disorders	1 (0.3)	3 (1)

SOC: System Organ Class

SAEs by SOC

C2301 and C2303: Placebo-controlled studies

Study C2301	TIP N=46	Placebo N=49
Total SAEs n (%)	3 (7)	7 (14)
Infections and infestations	0	2 (4)
Investigations	0	2 (4)
Respiratory, thoracic, and mediastinal	3 (7)	4 (8)

Study C2303	TIP N=30	Placebo N=32
Total SAEs n (%)	0	2 (6)
Injury (Lower limb fracture)	0	1 (3)
Respiratory, thoracic, and mediastinal (Pneumonia)	0	1 (3)

Fatal Events across All Studies

Study / Age / Gender	Received TIP	Cause of Death
C2301 / 10 yo / F	No	Decompensated chronic cor pulmonale
C2302 / 27 yo / F	No	Respiratory failure due to disease progression
C2302 / 21 yo / M	Yes	Pulmonary exacerbation leading to respiratory failure
C2302 / 24 yo / F	Yes	Acute respiratory failure secondary to pneumonia
C2302 / 25 yo / M	Yes	Hypoxic brain damage following accidental drug overdose (recreational)

Safety Agenda

- Review of TOBI® (inhalation solution) post-marketing experience
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- Overview of adverse events
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  - Local adverse reactions (cough, airway reactivity)
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Cough Adverse Events

C2302 (Primary Safety Population)

- Severity of reported cough

C2302	TIP (%)	TOBI (%)
Mild	23	15
Moderate	22	14
Severe	3	2
Serious	2	2

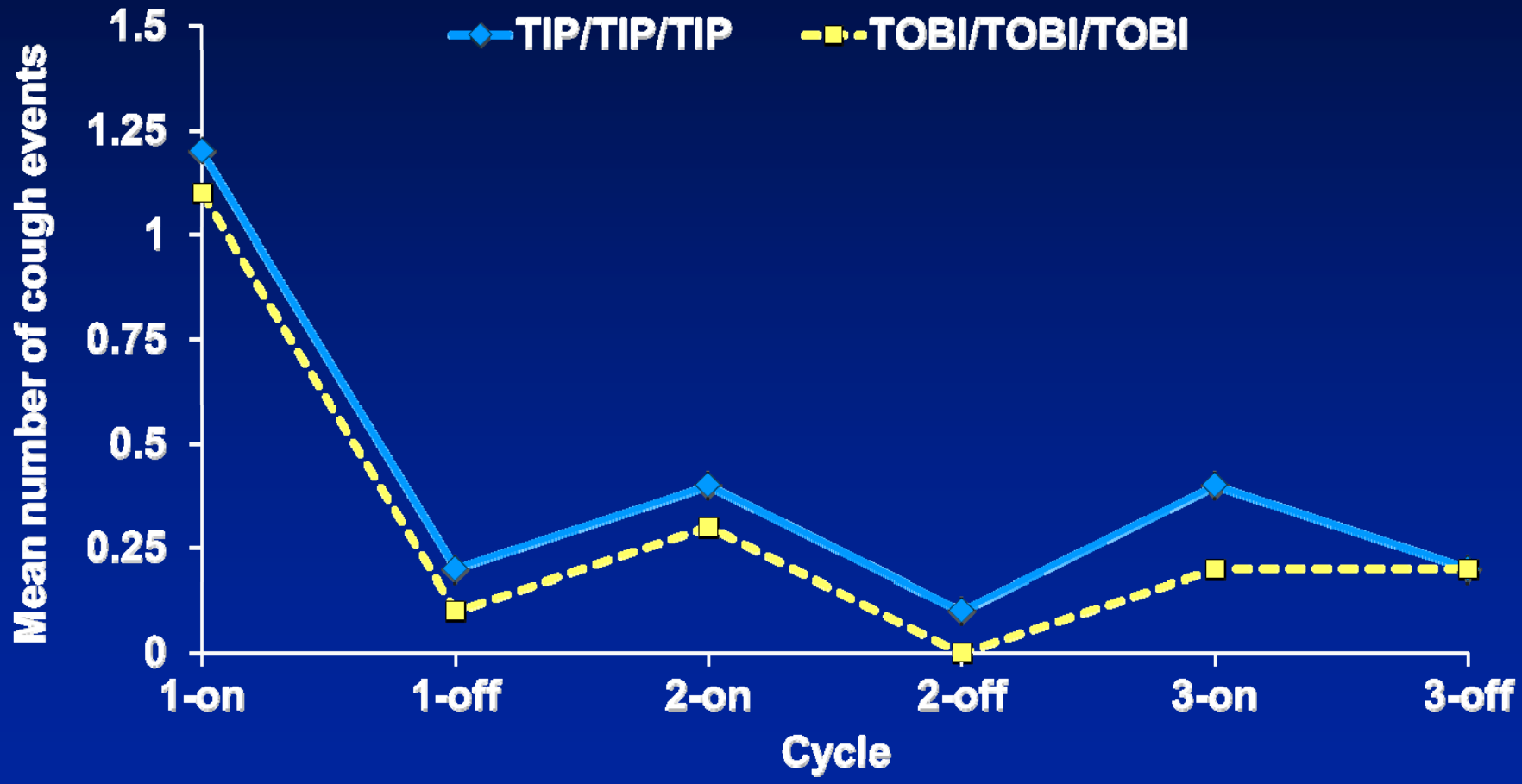
- Cough events occurred more frequently in the first treatment period
- Cough was the most frequent AE leading to discontinuation
  - Most discontinuations occurred in cycle 1 on treatment
  - 5 discontinuations due to cough as sole AE (1%)

C2301 and C2303 (placebo-controlled studies)

- Cough occurred in 12% of TIP vs. 16% placebo patients

For Patients with Cough in Cycle 1, Events Decreased over Time

C2302: Primary safety population



A cough event was counted for the on-/off-treatment period of a cycle if it started during the on-/off-treatment period of that cycle

Cough AE = adverse event preferred term containing "cough"

Airway Reactivity

FEV_1 decrease after inhalation (All studies)

- **Airway reactivity was defined as ≥20% decrease in FEV_1 % predicted from pre-dose to 30-minute post-dose, by treatment group**

Primary Safety Population	TIP n / total (%)	TOBI n / total (%)
Study C2302 – any cycle/visit	16 / 307 (5)	11 / 209 (5)

Placebo-controlled Studies	TIP n / total (%)	Pbo n / total (%)
Study C2301 – Cycle 1	1 / 32 (3)	4 / 37 (11)
Study C2303	0 / 30 (0)	4 / 32 (13)

- **No patient with airway reactivity reported a concomitant cough AE**

Airway Reactivity *(cont.)*

Bronchospasm AEs (All studies)

- **C2302 (primary safety population)**
  - **3 TIP patients discontinued due to AEs related to bronchospasm**
  - **Less than 10% decrease in FEV_1 % predicted at any visit**
- **C2301 and C2303 (placebo-controlled studies)**
  - **No discontinuations due to bronchospasm**

Cough and Airway Reactivity
Conclusions

- **Cough is an AE associated with tolerability but not airway reactivity**
  - **Mostly mild or moderate**
  - **Most discontinuations occur in first cycle**
- **TIP is not associated with increased airway reactivity compared to TOBI and placebo**

Safety Agenda

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Audiology in TIP Development Program

- Audiology performed in a subset of sites
- Acuity measured 0.25-8.0 kHz at baseline and after each treatment cycle
- Clinically significant hearing loss defined as:
  - 20 dB decrease at 1 frequency*
  - 10-15 dB at 2 consecutive frequencies**
- Hearing complaints solicited at every visit

* Based on American Speech Language Hearing Association criteria and TOBI registration studies

** Based on ASHA criteria 2009

Audiology Findings

C2302: Primary safety population

	TIP n=78 n (%)	TOBI n=45 n (%)
History of hearing events	15 (21)	6 (14)
Baseline abnormal audiograms	15 (20)	9 (21)
Clinically significant hearing loss during study*	4 (6)	3 (7)
Complaints related to hearing loss during study	11 (15)	5 (12)

* Change of 10-15 dB in at least 2 frequencies or 20 dB in one frequency that was sustained for at least 2 visits

Audiology Findings

C2301 and C2303: Placebo-controlled population

	TIP n=28 n (%)	Placebo n=21 n (%)
Baseline abnormal audiograms	4 (15)	0
Clinically significant hearing loss during study (NVS definition)*	3** (11)	1 (5)
Complaints related to hearing loss during study	3 (11)	2 (10)

* Change of 10-15 dB in at least 2 frequencies or 20 dB in one frequency

** 2 patients had normal audiograms at subsequent visit

Event Scales for Hearing Loss American Academy of Audiology*

- National Cancer Institute (NCI)
  - Grade 1: 15-25 dB relative to baseline at two or more contiguous frequencies
  - Grade 2: > 25-90 dB averaged at two contiguous test frequencies in at least one ear
  - Grade 3: Hearing loss sufficient to indicate therapeutic intervention
  - Grade 4: Indication for cochlear implant and requiring additional speech language related services (bilateral hearing loss >90 db)
- Brook's Hearing Loss Guide
  - Grade 0: < 40 dB at all frequencies
  - Grade 1: ≥ 40 dB at 8000 Hz
  - Grade 3: ≥ 40 dB at 2000-80000 Hz
  - Grade 4: ≥ 40 dB at 1000-8000 Hz

* American Academy of Audiology: Physician Statement and Clinical Practice Guidelines: Ototoxicity Monitoring, October 2009

Renal Effects

C2301, C2302, and C2303

C2302	TIP N=308 n (%)	TOBI N=209 n (%)
Increase in CR >50% baseline	15 (5)	8 (4)
Increase in CR >ULN	2 (1)	2 (1)
Proteinuria*	5 (2)	3 (1)

* 1+ or greater proteinuria at consecutive visits

- C2301: No significant renal function changes or renal AEs
- C2303: 1 non-serious renal AE TIP patient with 2+ proteinuria at day 29

Renal Effects Similar between TIP, TOBI, and Placebo Treatment Arms

Conclusions

- **In phase 3 studies, renal effects of TIP were minimal and similar to TOBI and placebo**

Safety Agenda

- Review of TOBI® (inhalation solution) post-marketing experience
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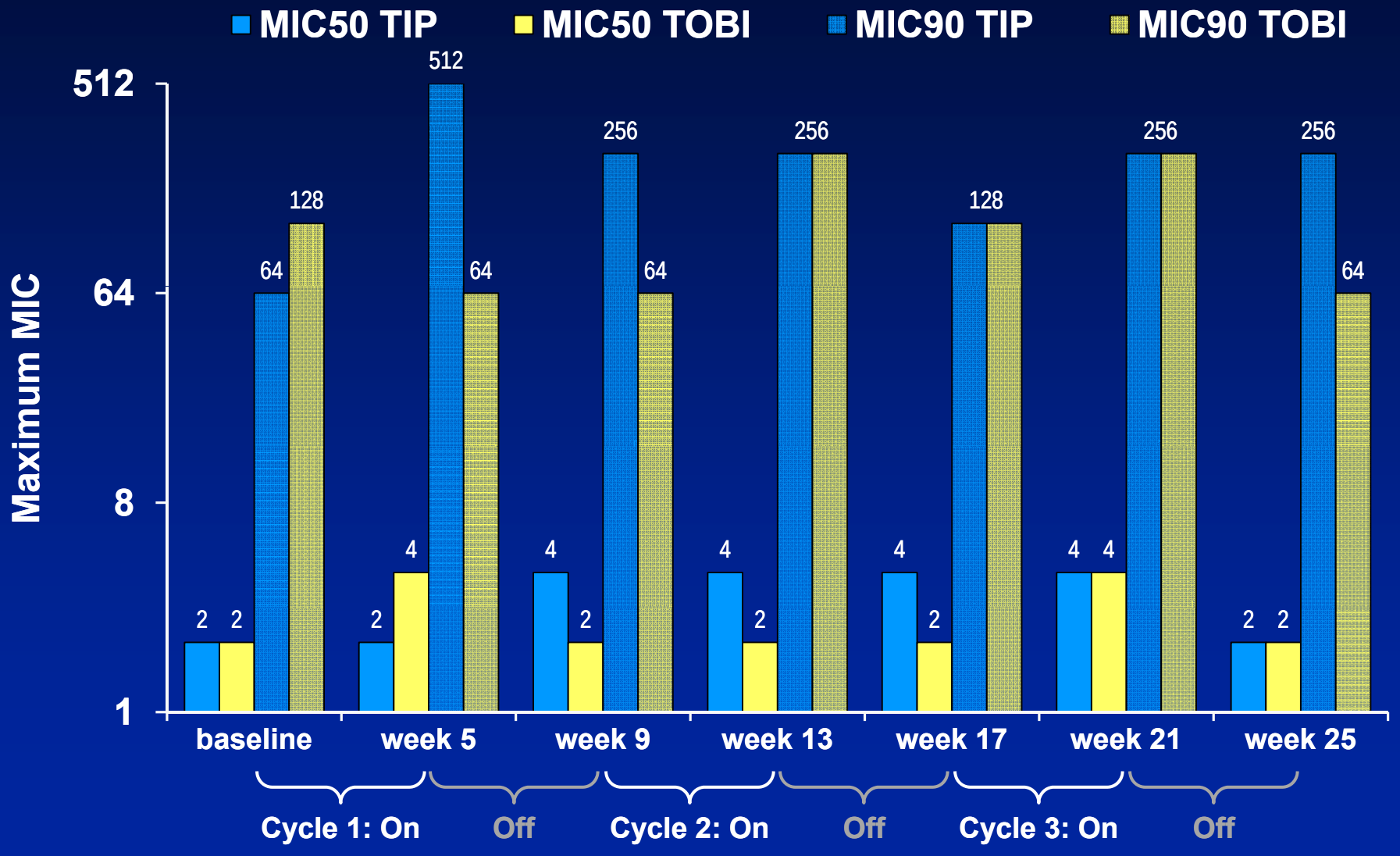
- Overview of adverse events
- **Areas of special interest**
  - Local adverse reactions (cough, airway reactivity)
  - Systemic adverse reactions (ototoxicity, renal effects)
  - **Microbiology (changes in MIC, treatment emergent organisms)**
- Post-approval experience of TIP

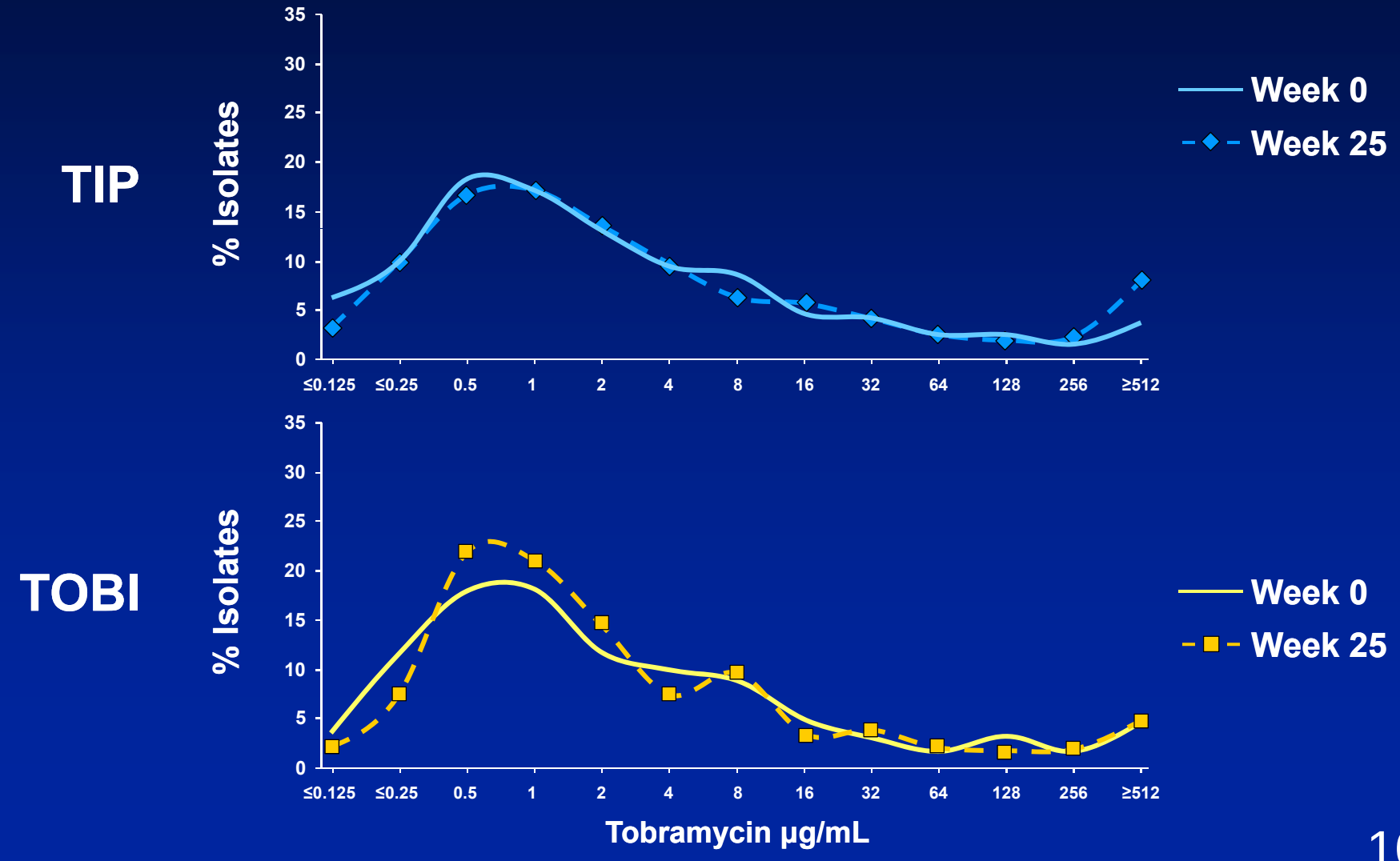
Variation of MIC_{50} and MIC_{90} over Time

C2302: Primary safety population



Distribution of Tobramycin MICs/ All *P. aeruginosa* Isolates

C2302: Primary safety population



Clinical Outcomes Similar among Patients with High MIC Isolates

C2302: Primary safety population – baseline to week 25

	TIP/TIP/TIP N=308		TOBI/TOBI/TOBI N=209			
FEV_1 Change	n*	LSMean	n	LSMean	Difference	95% CI
<8 µg/mL	179	3.7	135	1.7	2.0	(-2.2, 6.1)
≥128 µg/mL	18	3.6	18	5.5	-1.9	(-13.9, 10.2)

Hospitalization Rate	n*	n (%)	n	n (%)	OR	95% CI
<8 µg/mL	240	58 (24)	160	35 (22)	1.1	(0.7, 1.8)
≥128 µg/mL	27	5 (19)	24	6 (25)	0.7	(0.2, 2.6)

* n = patients with eligible data at baseline

LSMean = Adjusted mean for covariates (least square mean)

Treatment-Emergent Pathogens*

C2302: Primary safety population Organism	TIP N=308 n (%)	TOBI N=209 n (%)
S. maltophilia	16 (5)	8 (4)
A. xylosoxidans	4 (1)	6 (3)
S. aureus	11 (4)	7 (3)
MRSA	4 (1)	5 (2)
Aspergillus fumigatus	14 (5)	10 (5)

Placebo-controlled studies	C2301 (cycle 1)		C2303	
Organism	TIP N=46 n (%)	Placebo N=49 n (%)	TIP N=30 n (%)	Placebo N=32 n (%)
S. maltophilia	0	0	1 (3)	0
A. xylosoxidans	0	0	0	0
S. aureus	0	1 (2)	0	1 (3)
MRSA	1 (2)	0	0	0
Aspergillus fumigatus	0	0	0	0

* Not present at screening or baseline and present in 2 or more sputum cultures post-treatment

Microbiology Summary

- Distribution of tobramycin MICs were generally comparable
- MIC_{50} did not change during the study
- MIC_{90} did not rise consistently over time
- Small numbers of patients account for elevated MICs at week 25
- Clinically meaningful outcomes are similar among patients with MIC <8 µg/mL compared to ≥128 µg/mL
- Similar treatment-emergent pathogens in all treatment groups

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- Post-approval experience of TIP

No New Adverse Drug Reactions in TIP Post-approval Experience*

- The patient exposure of TIP since first approval is approximately 1,217 patient-treatment years
- 136 spontaneous reports

Most Common AEs	N
Cough	57
Dysphonia	22
Dyspnea	22
Chest discomfort	15

Most Common SAEs	N
Lung Infection	7
Dyspnea	7
Hemoptysis	5
Cough	5

- In C2303E1, the most common AEs are cough and respiratory tract infection

* As of 30Jun12

TIP Is an Important Option for the Treatment of Cystic Fibrosis

- **Benefits**
  - **TIP shows sustained efficacy across 3 cycles**
    - **C2301 and C2303 Extension 1 study**
  - **TIP provides *P. aeruginosa* suppression, decreased hospitalizations, and less antibiotic use vs. placebo**
  - **TIP decreases the burden of treatment vs. TOBI**
    - **1 hour/day, 7 hours/week, ~1 week/year in administration time**
- **Risks**
  - **Local adverse effects (cough, dysphonia, dysgeusia) decrease over time**
  - **Systemic adverse effects similar to TOBI**

TIP: A Clinician's Perspective

Patrick A. Flume, MD

Professor,
Pulmonary and Critical Care Medicine

Medical University of South Carolina

Disclosures

Grant Support

Mpex Pharmaceuticals, Inc

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Cystic Fibrosis Foundation

National Institutes of Health

Consultant

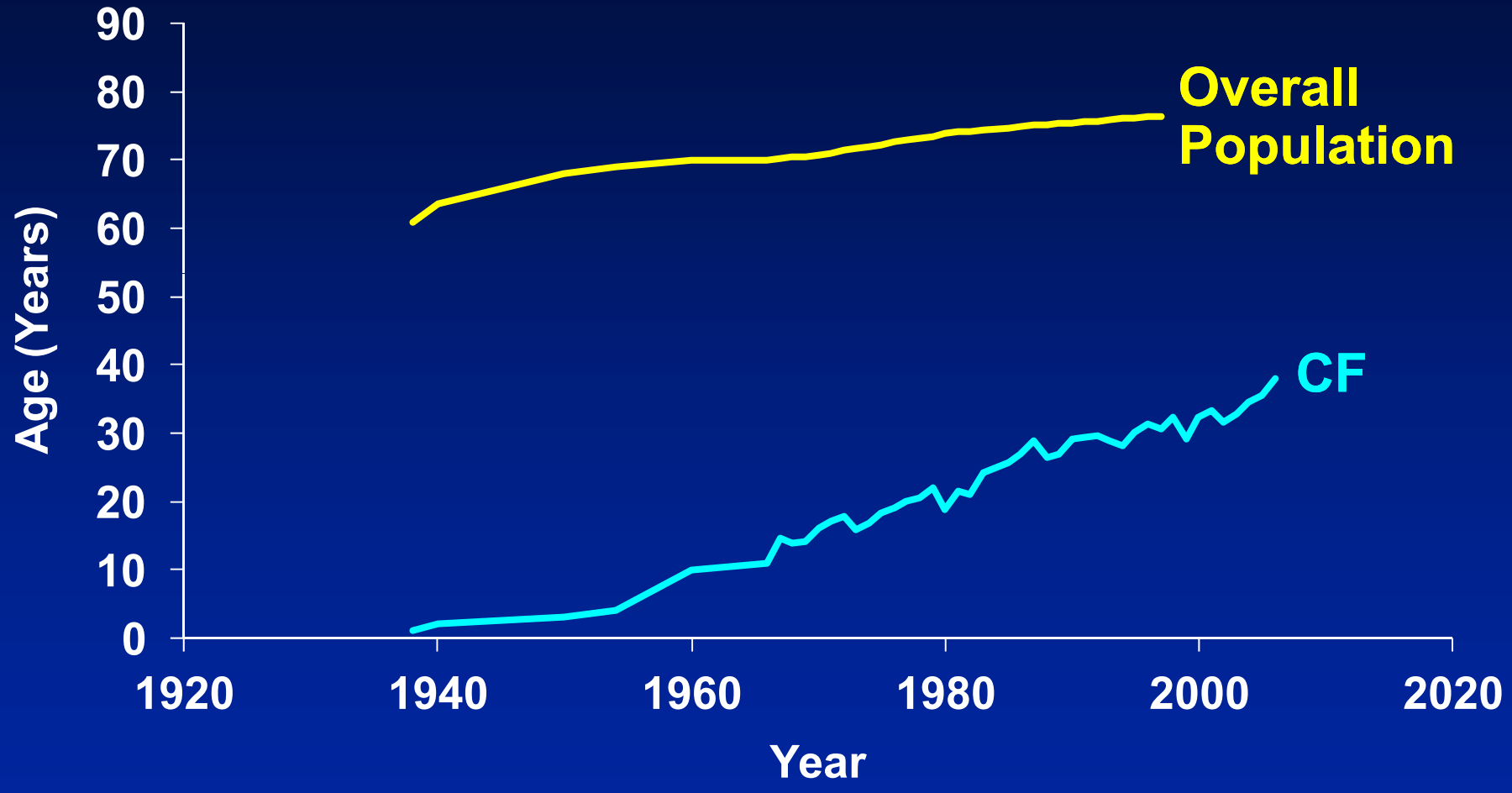
Gilead

Novartis

Vertex Pharmaceuticals, Inc

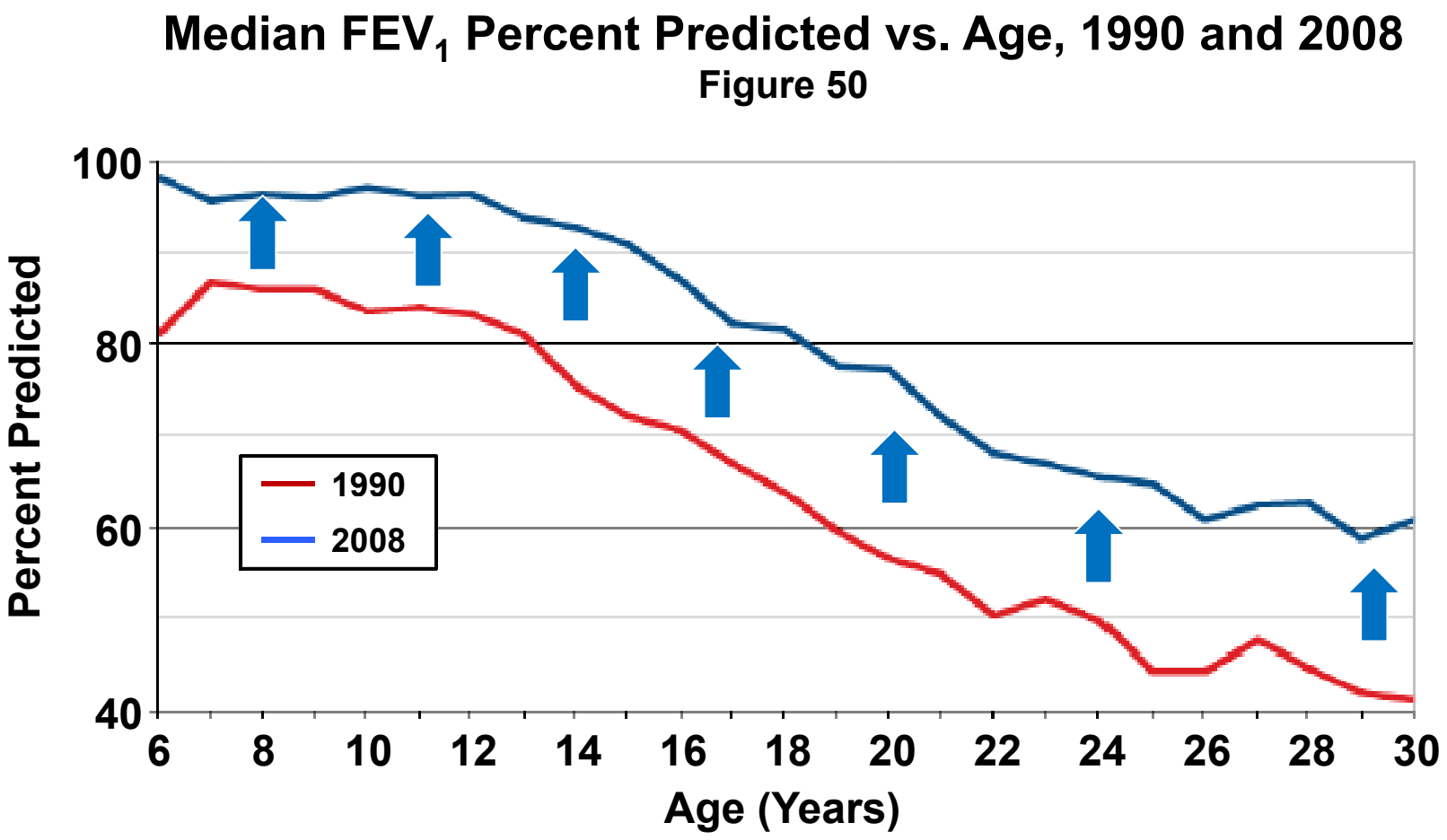
Speaker's Bureau

Median Age of Survival in CF



CFF Patient Registry, 2010 Annual Data Report Bethesda, Maryland © 2011 Cystic Fibrosis Foundation
US Census Data

Pulmonary Function Is Improving



Chronic Therapies for Maintenance of Lung Health

A Strong Recommendation for:	B Recommendation for:	D Recommendation against:
• Inhaled tobramycin – Mod-severe dz	• Inhaled tobramycin – Mild-asx dz	• Oral steroids – Age 6-18
• Dornase alfa – Mod-severe dz	• Dornase alfa – Mild-asx dz	• Inhaled steroids
	• Hypertonic saline	• Anti-Staph abx
	• Macrolides	
	• Ibuprofen	
	• Inhaled β-agonists	

Insufficient Evidence to make a recommendation:

- Other aerosolized antibiotics
- N-acetyl cysteine
- Cromolyn
- Inhaled anticholinergics
- Leukotriene modifiers
- Oral steroids (age>18)

Flume, PA et al. Am J Respir Crit Care Med 2007; 176: 957-969

A Day in the Life

Poor Adherence Leads to Increased Hospitalization Risk and Treatment Failure

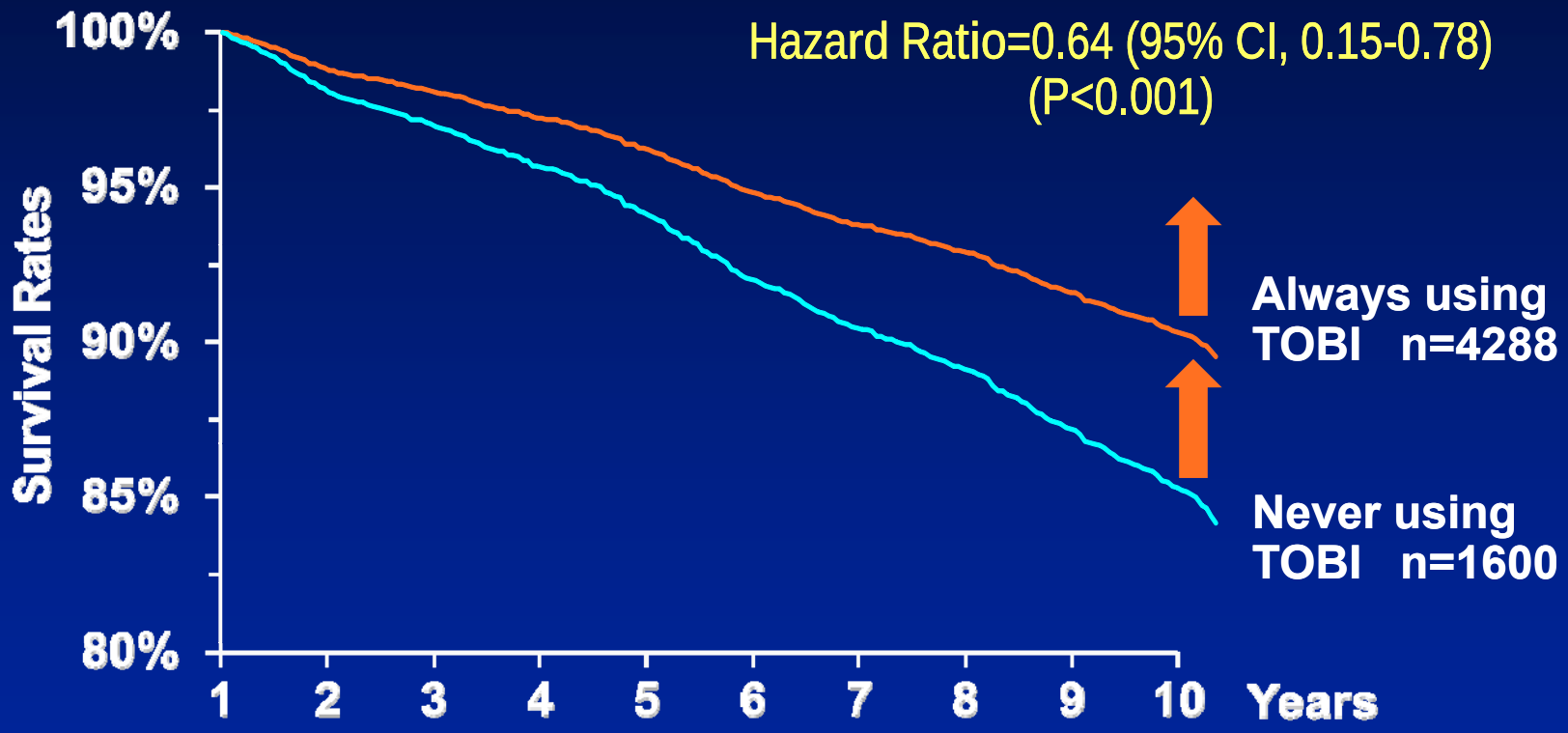
Logistic regression of probability of hospitalization of CF patients (N=804)			
Overall adherence with TOBI	**Utilization**	**OR***	**95% CI**
Low (≤2 cycles) (n=570)	71%	1.0	
Medium (>2 to <4 cycles) (n=180)	22%	0.94	0.62–1.41
High (≥4 cycles) (n=54)	6%	0.40	0.19–0.84

- **High adherence reduces hospitalization by 60%[1]**
- **Poor adherence may limit clinical benefits that inhaled tobramycin can offer**

[1] Briesacher BA, et al. *BMC Pulmonary Medicine 2011, 11:5*.

* Adjusted for variables in the table and health plan type and geographic residence

Long-Term TOBI Use Results In a 36% Reduction in Mortality*



*Analysis of data from CFF registry from 1996-2008

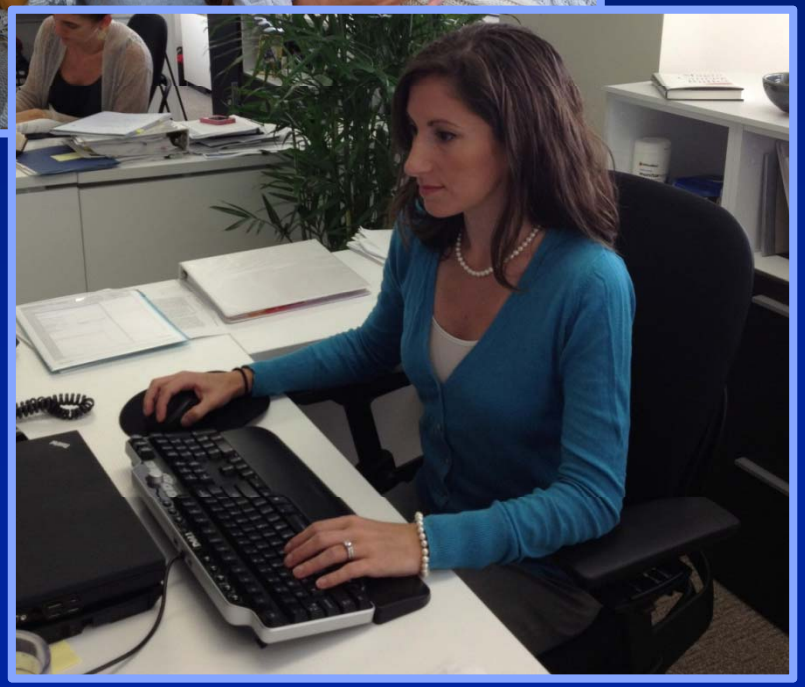
Sawicki, et al. *Ped Pulm* (2011) 1-9

Why Do We Need TIP?

- TIP is tobramycin
  - It offers the same benefits as TOBI
    - Similar improvement in lung function
    - Similar rates of respiratory related hospitalizations
- But, this is the option we've been waiting for
  - Easy
  - Portable
  - Faster
  - Liberating

A Clinician's Perspective

- We need aerosolized antibiotic options



Q&A Slides Presented

FDA CDER

FDA Anti-Infective Drugs Advisory Committee Meeting

September 5, 2012

C2302: Alternate Confidence Coefficient Non-inferiority Investigation

- TOBI minus placebo estimated effect size:

  8.82%, s.e. = 2.29%

- One-sided lower 97.5% confidence limit: 4.33%
- 95% 2-sided confidence limit for TIP minus TOBI:

  (-2.30%, 4.59%)

- -2.30 > -4.33, so non-inferiority is achieved

Study C2302

Cough AEs Post-TIP Inhalation by Verbatim Term*

- Severity of reported cough event

Total	29
Mild	21
Moderate	6
Severe	2
Leading to D/C	3
Serious	0

*Included verbatim terms of: increased cough after treatment, increased cough during inhalation, cough after inhalation, cough drug treatment with study drug, cough associated with study drug, cough after pills, worsening cough after TIP inhaled

Lung Function, Cough Score Similar between TIP and TOBI

- No significant differences in lung function between the TIP vs. TOBI group to date

FEV_1% predicted	TOBI	TIP [+]
Median	64.5	67
Mean	62.8	62.8

[+] based on last observation carried forward.

- Cough scores were similar (mild to moderate) with no significant difference between the TIP vs. TOBI group to date

- Subgroup (n=20) 6-month IV antibiotics usage pre- and post- transition from TOBI to TIP:
  - 10 courses pre-TIP vs. 5 courses post-TIP

TIP Patients Reported Excellent Compliance and All Preferred TIP

- Significant improved compliance observed on TIP (p= 0.001)

Compliance score: 1 poor to 3 excellent	TOBI At study enrolment	TIP +
Mean	2.1	2.9

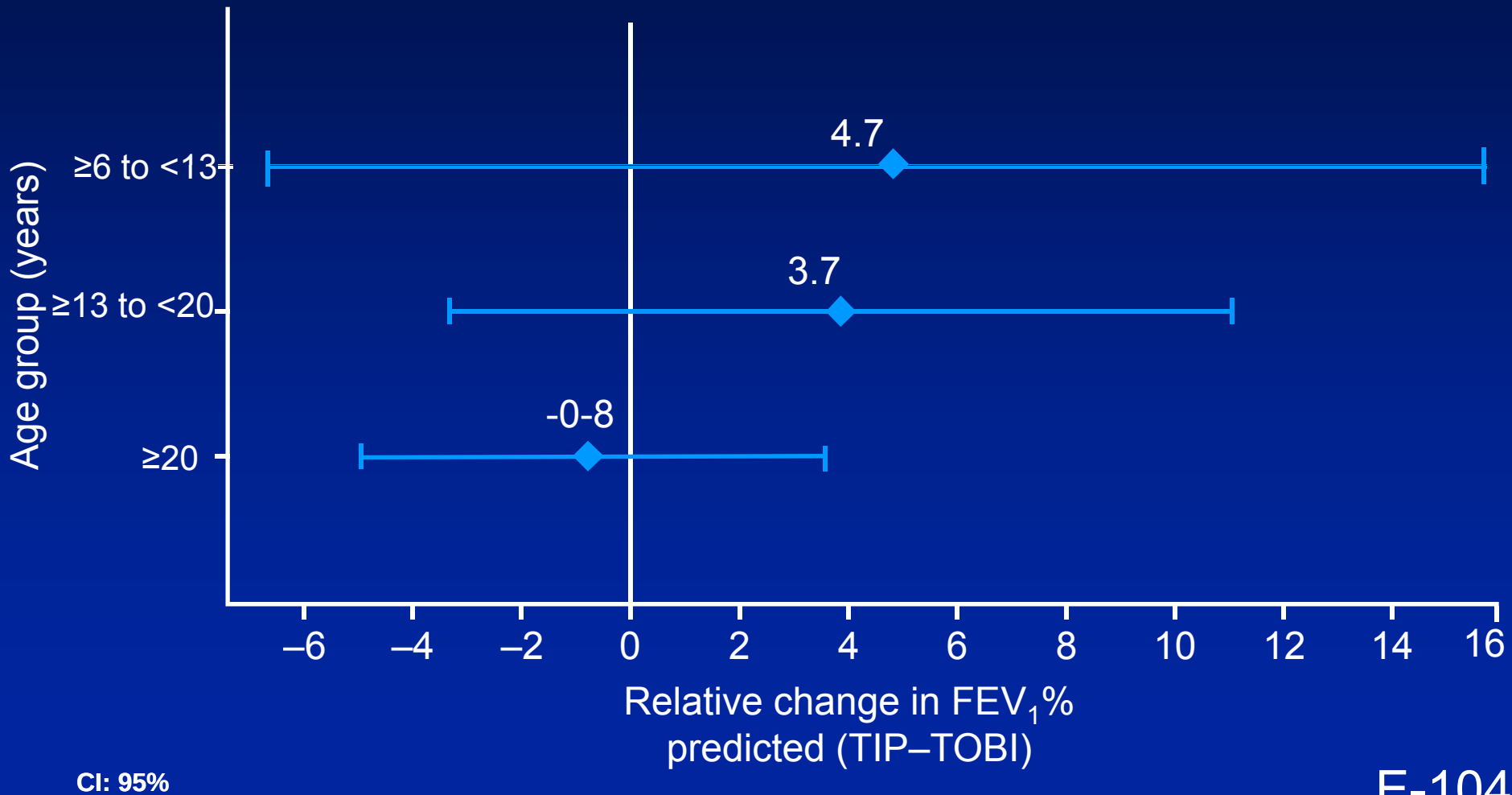
+ based on last observation carried forward.

- No patient reported decreased compliance on TIP

  - 36/41 (88%) reported excellent compliance on TIP
  - 20/48 (42%) reported excellent compliance on TOBI

- All patients preferred TIP at all data points citing *"time-saving"* and *"convenience"* vs. TOBI as the most common reasons

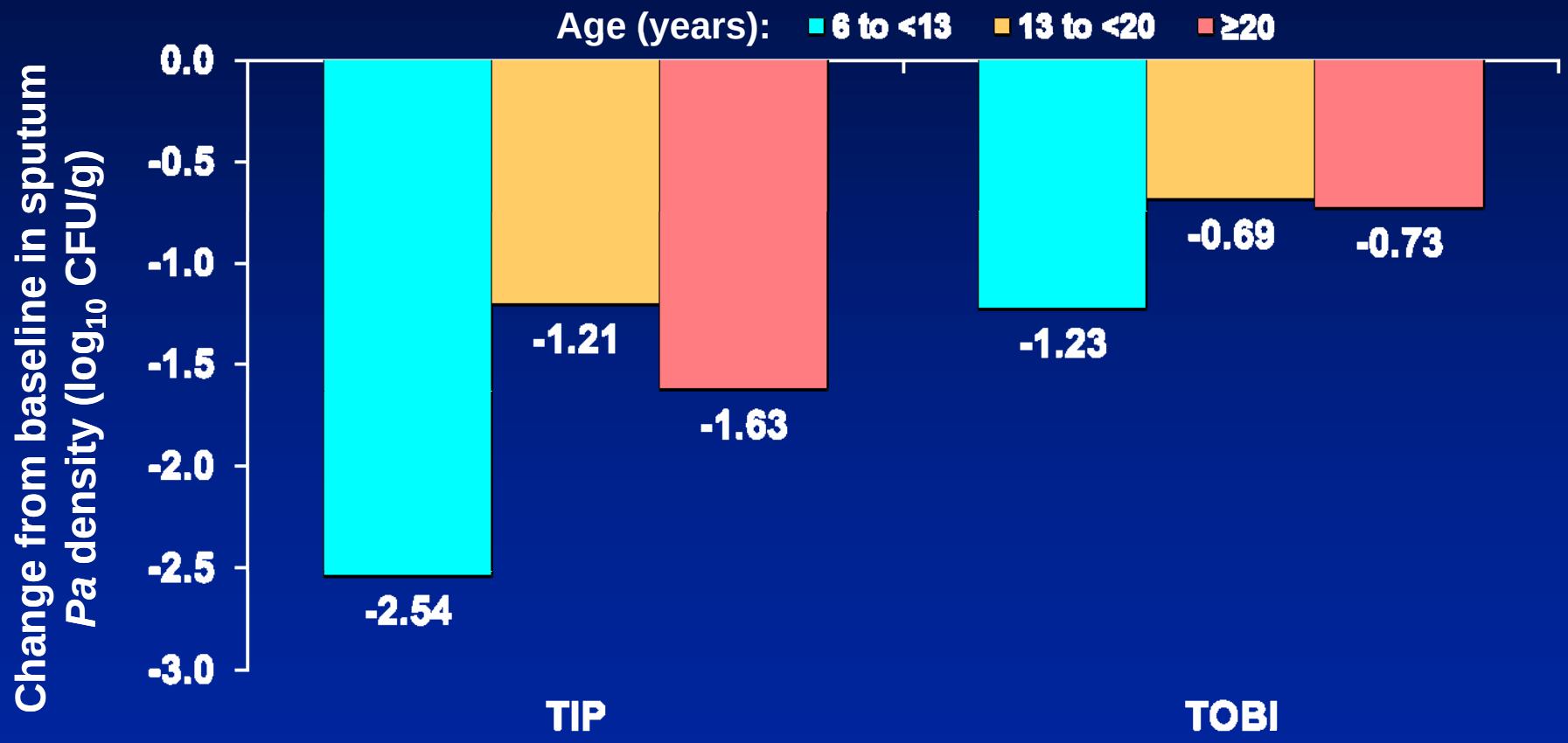
C2302: Relative Change in FEV_1 % Predicted from Baseline to End of Dosing in Cycle 3



CI: 95%

E-104

C2302: Reduction in Sputum Density of *Pa* with TOBI and TIP (Age-group Analysis)



Study 2302

Patients with Maximum MICs ≥ 16µg/mL

	TIP		TOBI	
Visit	N	n (%)	N	n (%)
Baseline	308	68 (22.1)	208	48 (23.1)
Cycle 1- end on (week 5)	239	69 (28.9)	173	43 (24.9)
Cycle 1- end off (week 9)	242	66 (27.3)	174	41 (23.6)
Cycle 2- end on (week 13)	215	74 (34.4)	157	42 (26.8)
Cycle 2- end off (week 17)	221	65 (29.4)	161	42 (26.1)
Cycle 3- end on (week 21)	199	64 (32.2)	154	48 (31.2)
Cycle 3- end off (week 25)	201	60 (29.9)	155	32 (20.6)

Study 2302

Maximum MICs ≥512 µg/mL per Patient

	TIP		TOBI	
Visit	N	n (%)	N	n (%)
Baseline	308	13 (4.2)	208	10 (4.8)
Cycle 1-end on (week 5)	239	26 (10.8)	173	12 (6.9)
Cycle 1- end off (week 9)	242	22 (9.1)	174	8 (4.6)
Cycle 2- end on (week 13)	215	20 (9.4)	157	13 (8.3)
Cycle 2- end off (week 17)	221	16 (7.2)	161	11 (6.8)
Cycle 3- end on (week 21)	199	18 (9.0)	154	12 (7.8)
Cycle 3- end off (week 25)	201	19 (9.5)	155	9 (5.8)

Study C2301

Maximum MICs ≥512 µg/mL

	TIP/TIP/TIP	
Cycle (week)	N	n (%) at visit
Baseline	44	2 (4.6)
Cycle 1-end on (week 5)	29	3 (10.3)
Cycle 1- end off (week 9)	32	2 (6.3)
Cycle 2- end on (week 13)	29	4 (13.8)
Cycle 2- end off (week 17)	33	3 (9.1)
Cycle 3- end on (week 21)	28	3 (10.7)
Cycle 3- end off (week 25)	30	2 (6.7)

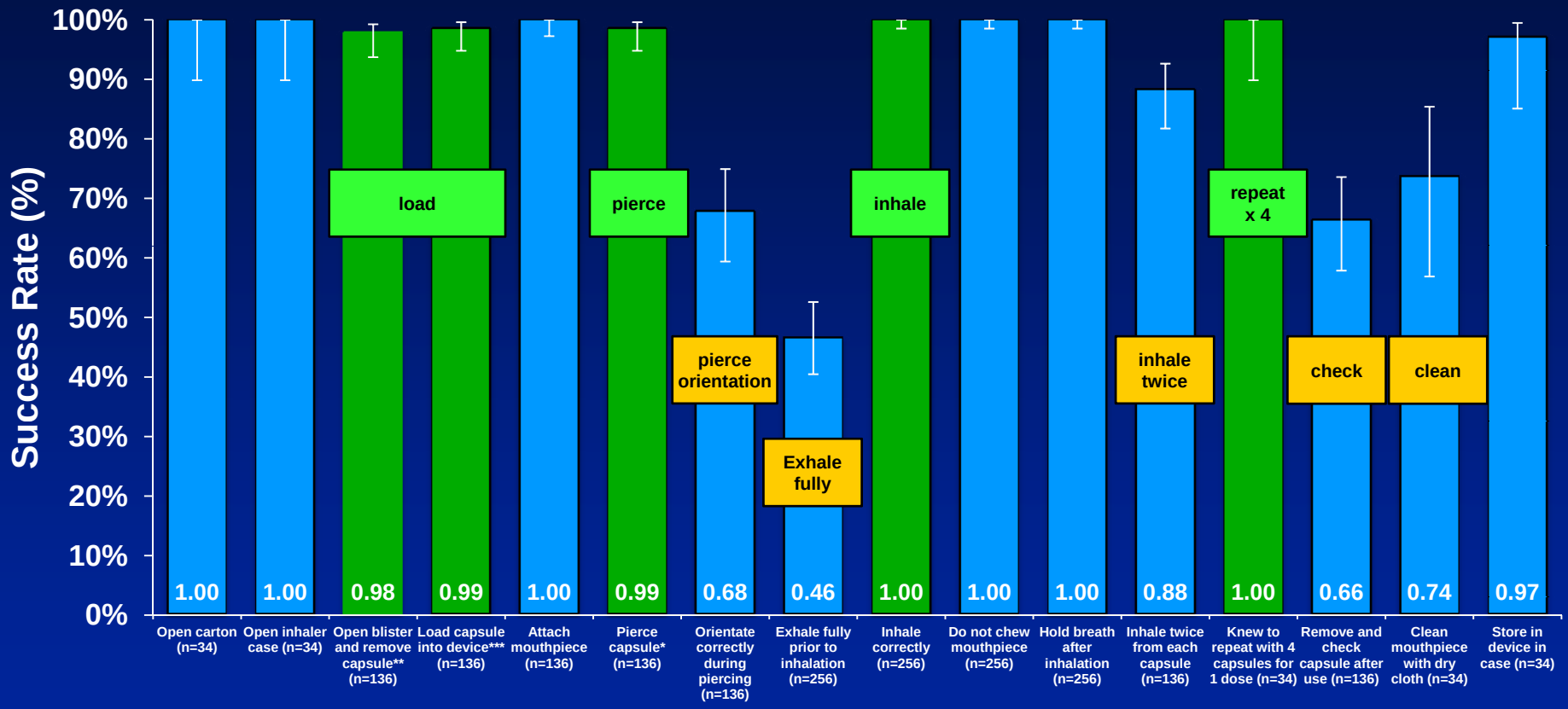
Podhaler – A Well Understood Inhaler Design

"Load, Pierce & Inhale" capsule inhalers are common

- **First capsule inhaler launched in 1967**
  - **e.g. Spiriva Handihaler / Arcapta Neohaler currently on market in US**
- **Identical critical steps to achieve dosing:**
  - **Load capsule into inhaler**
  - **Pierce capsule by pressing button/s**
  - **Inhale to aerosolize powder and transport to lung**
- **Podhaler conforms with this common inhaler interaction design**

Summary of Observed User Task Performance

Post 1-week use assessment – US study



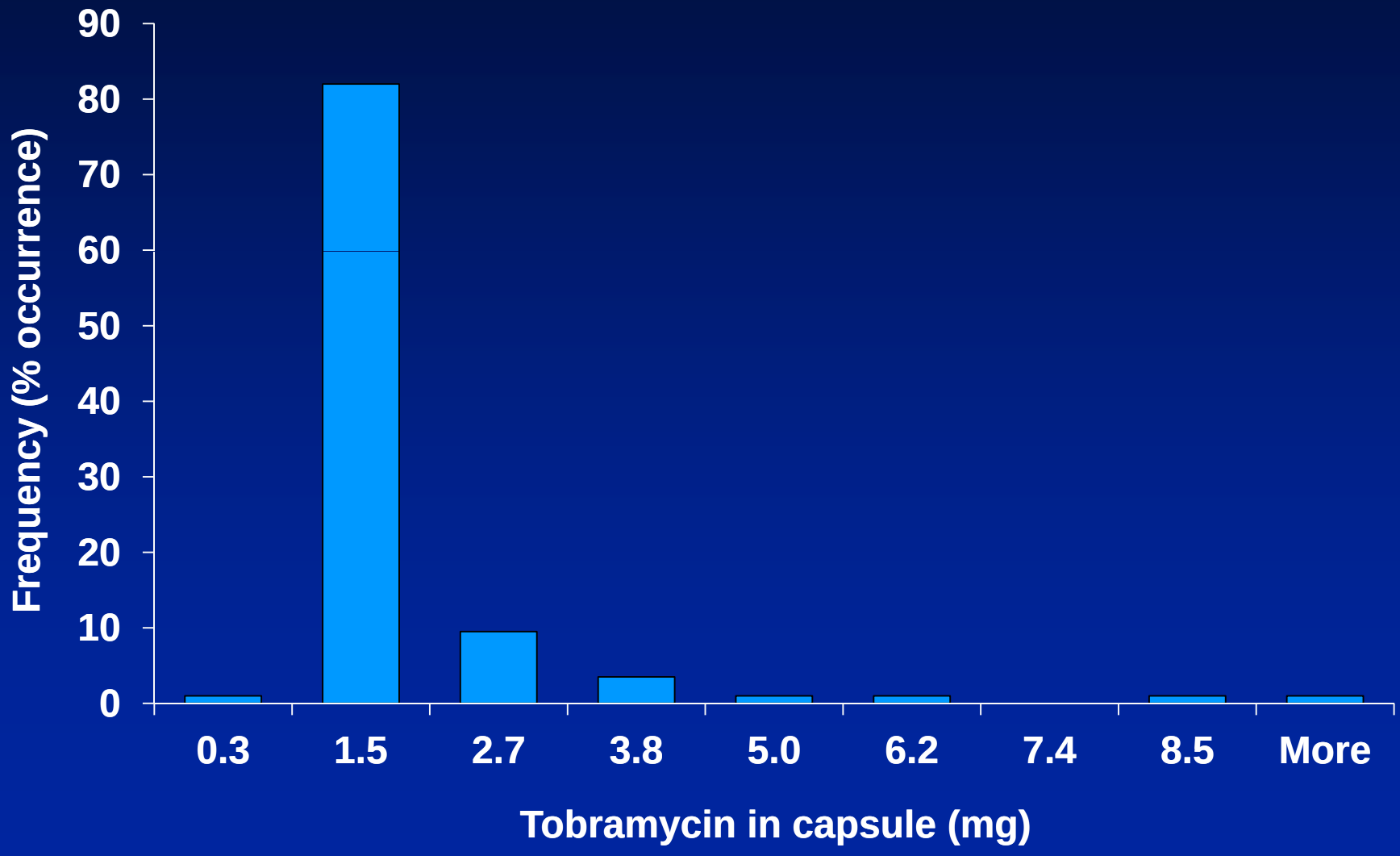
Error bars indicate the upper and lower limits of a two-sided Wilson binomial confidence interval (p=0.05).

*** Capsule inspection data**

**** Capsules dropped during removal from blister**

***** Capsules dropped during loading into inhaler**

Residual Tobramycin (Per 28 mg Capsule)



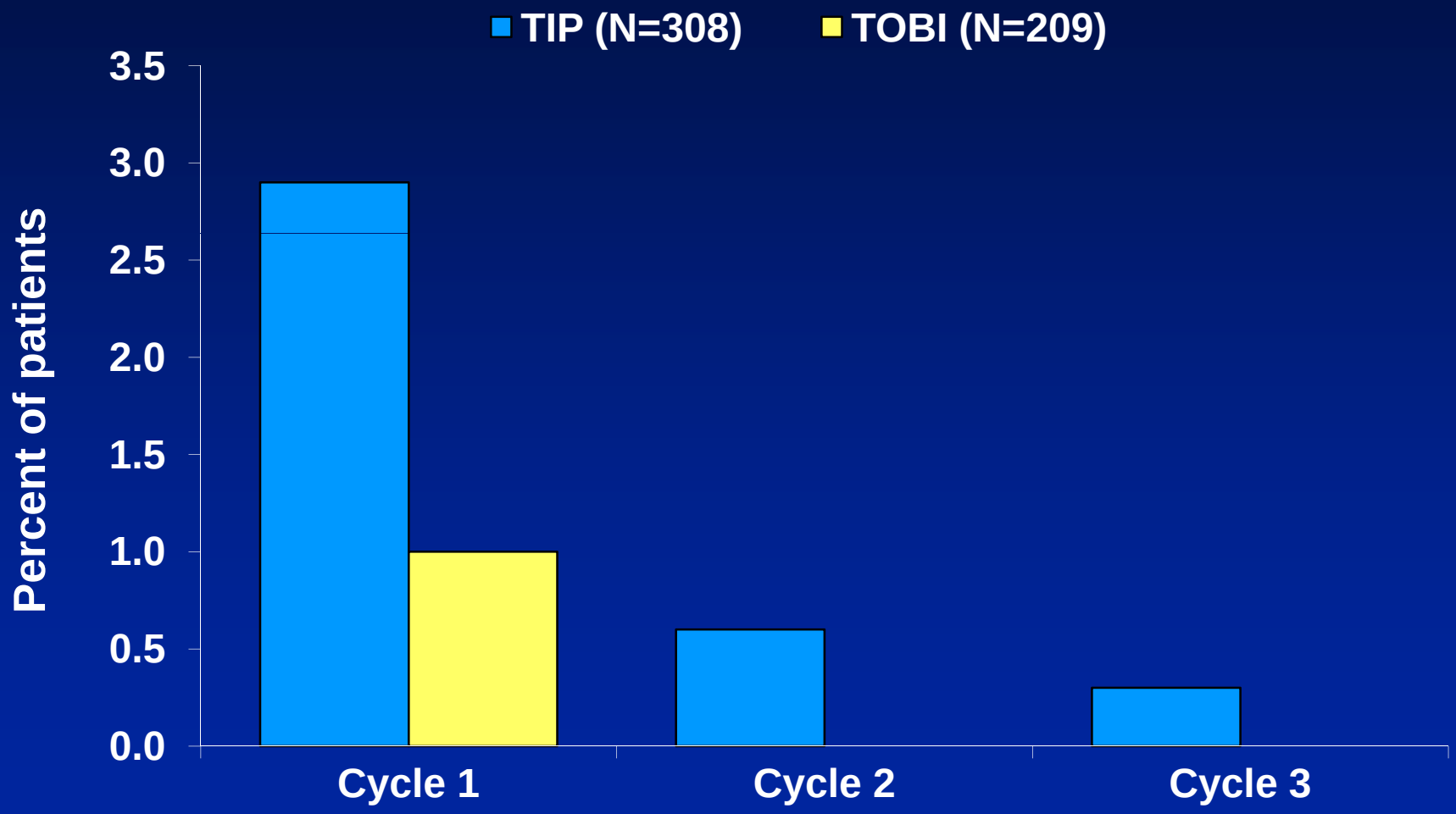
C2301: Baseline Demographics

All randomized safety population

	TIP (n=46)	Placebo (n=49)	Total (n=95)
Age, years			
Mean (SD)	13.4 (4.42)	13.2 (3.91)	13.3 (4.14)
Median (min–max)	14.0 (6.0-21.0)	13.0 (6.0-21.0)	13.0 (6.0-21.0)
Age category, n (%)			
≥6 - <13	21 (45.7%)	24 (49.0%)	45 (47.4%)
≥13 - < 22	25 (54.3%)	25 (51.0%)	50 (52.6%)
Sex, n (%)			
Male	19 (41.3%)	23 (46.9%)	42 (44.2%)
Female	27 (58.7%)	26 (53.1%)	53 (55.8%)
Race, n (%)			
Caucasian	37 (80.4%)	43 (87.8%)	80 (84.2%)
Hispanic	8 (17.4%)	4 (8.2%)	12 (12.6%)
Other	1 (2.2%)	2 (4.0%)	3 (3.2%)
Weight, kg			
Mean (SD)	37.1 (14.68)	38.4 (12.45)	37.8 (13.52)
Median (min–max)	36.3 (18.8 -75.9)	37.9 (14.2 – 61.4)	37.0 (14.2 – 75.9)
Height, cm			
Mean (SD)	146.1 (17.41)	147.7 (16.25)	146.9 (16.75)
Median (min–max)	150.8 (115.0- 180.5)	149.0 (106.0 – 173.5)	150.0 (106.0 – 180.5)

Study C2302

Patients with Cough Leading to Discontinuation by Cycle



C2302: FEV_1 % Predicted Relative Change from Baseline to End of Dosing Cycle 3

	TIP/TIP/TIP N=308			TOBI/TOBI/TOBI N=209			Difference (TIP-TOBI)	
Subgroup	n	Mean (SD)	LS Mean	n	Mean (SD)	LS Mean	LS Mean (SE)	CI
Region								
Europe/ROW	76	5.5 (20.33)	5.4	61	6.2 (17.26)	6.3	-0.9 (3.08)	(-6.9, 5.2)
Latin America	8	24.9 (40.29)	23.7	7	7.8 (21.61)	0.1	23.6 (9.36)	(5.2, 42.0)
North America	143	0.6 (17.24)	1.0	103	-0.4 (17.11)	-0.3	1.3 (2.32)	(-3.3, 5.8)

Least squares mean, least square mean difference, and its 95% confidence interval are from ANCOVA model (Relative change in FEV_1 % predicted – treatment + baseline FEV_1 % predicted (continuous) + subgroup + subgroup-by-treatment interaction). Note when subgroup is baseline FEV_1 % predicted (<50%, ≥50%), baseline FEV_1 % predicted (continuous) won't be included in the model. ROW = rest of world

C2302: FEV_1 % Predicted Relative Change from Baseline to End of Dosing Cycle 3

	TIP/TIP/TIP N=308			TOBI/TOBI/TOBI N=209			Difference (TIP-TOBI)	
Subgroup	n	Mean (SD)	LS Mean	n	Mean (SD)	LS Mean	LS Mean (SE)	CI
Baseline FEV_1 % predicted								
< 50%	77	10.1 (25.42)	10.1	76	6.1 (19.83)	6.1	4.0 (2.99)	(-1.9, 9.8)
≥ 50%	150	-0.5 (15.31)	-0.5	95	-0.7 (14.94)	-0.7	0.2 (2.42)	(-4.5, 5.0)

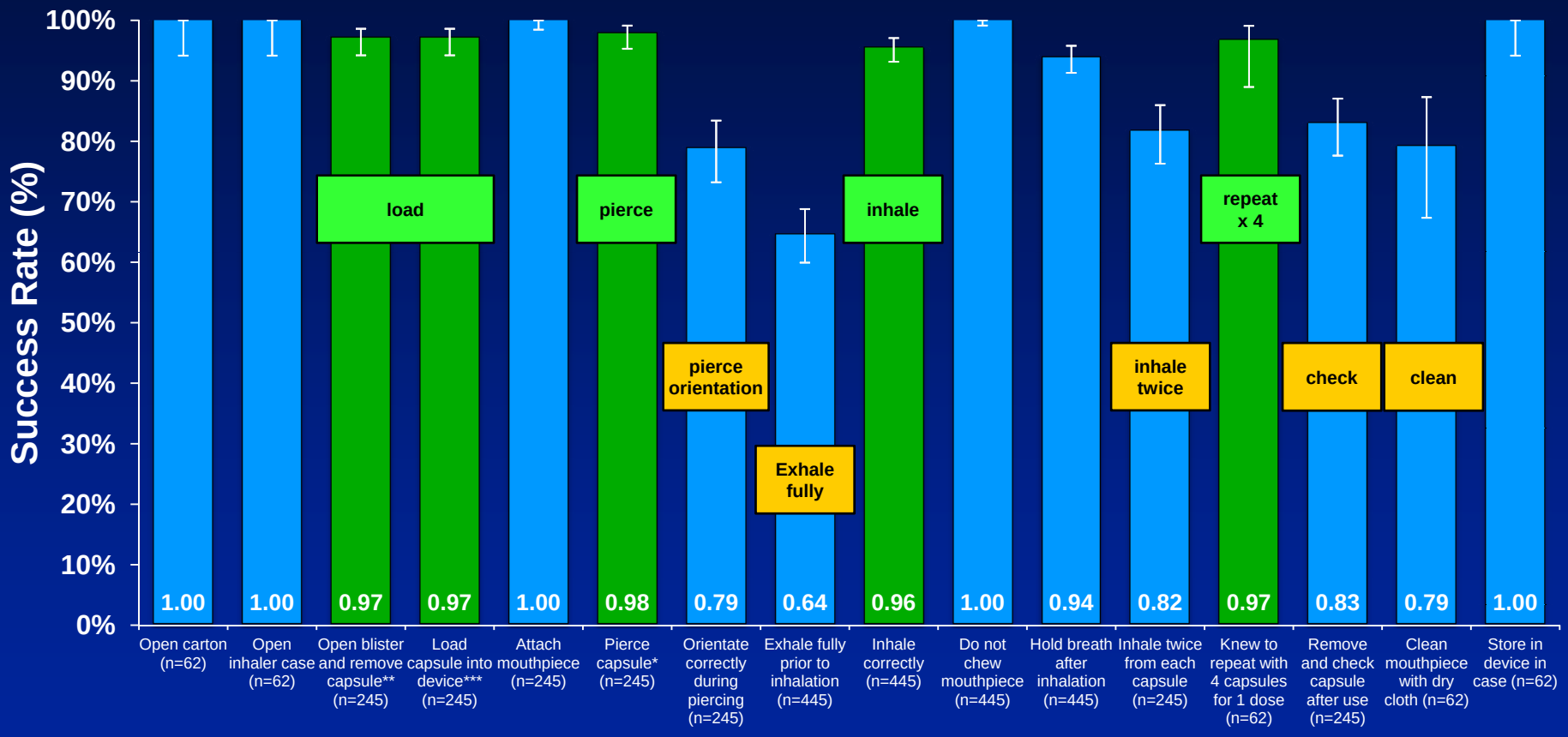
Least squares mean, least square mean difference, and its 95% confidence interval are from ANCOVA model (Relative change in FEV_1 % predicted – treatment + baseline FEV_1 % predicted (continuous) + subgroup + subgroup-by-treatment interaction). Note when subgroup is baseline FEV_1 % predicted (<50%, ≥50%), baseline FEV1 % predicted (continuous) won't be included in the model. ROW = rest of world

DSPC Delivered to the Lung Is Much Lower for TIP Than Other Approved Products

- **Delivered dose of phospholipid in exogenous surfactants**
  - **Total PC: Survanta: 62 mg/kg; Curosurf: 138 mg/kg**
  - **DSPC: Survanta: 2.7 mg/kg; Curosurf: 8 mg/kg**
- **Delivered dose of DSPC in TIP**
  - **DSPC: 0.37 mg/kg/day (assuming 50 kg bw and 34% lung delivery)**
  - **TIP delivers about 0.6% and 0.3% of the PC in Curosurf and Survanta to the lungs, and 13.7% and 4.6% of the total DSPC**

Summary of Observed User Task Performance

First time use – US study



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