U.S. FOOD & DRUG ADMINISTRATION

FDA Opening Remarks

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Division of Anti-Infective Products
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Introduction

- NDA 210693: Ciprofloxacin dispersion for inhalation (DI); Linhaliq
- Applicant: Aradigm Corporation
- Proposed indication: Treatment of non-cystic fibrosis bronchiectasis (NCFB) patients with chronic lung infections with *Pseudomonas aeruginosa*
- Dosage form and strength: Vials containing ciprofloxacin liposome inhalation suspension (135mg free base/3mL) and ciprofloxacin inhalation solution (54 mg free base/3mL) co-packaged for oral inhalation use with nebulizer
- Proposed dosing regimen: 189 mg once daily in 28 day on/off cycles

Development Program

- One phase 2 trial and two phase 3 trials in patients with NCFB
- Reasons for conducting two phase 3 trials to support NCFB indication
  - There are no approved therapies for prevention or management of NCFB exacerbations
  - Studies of other inhaled antibacterial drugs (tobramycin, gentamicin, aztreonam, colistin, and ciprofloxacin) for the prevention of NCFB exacerbations have yielded mixed results*
  - Uncertainties regarding duration of treatment, frequency of administration, and appropriate endpoints for this use with no prior successful trials
  - No relevant animal models of NCFB to explore dosing regimen, duration of therapy, and to provide supportive information
  - New indication and route of administration for ciprofloxacin
  - Two independent trials would provide replicative evidence of efficacy
  - Need for adequate safety assessment

*Publications referenced in FDA briefing document

Phase 2 Trial: ORBIT-2 (0902)

- Randomized, double-blind, multicenter trial comparing treatment with ciprofloxacin DI 189 mg once daily (n=20) vs. placebo (n=22) for 3 28-day on/off cycles
- Primary efficacy variable: change in sputum *P. aeruginosa* load (log_{10} CFU/g) from baseline to day 28
- Mean log_{10} CFU/g reduction at day 28: -4.20 for ciprofloxacin DI, -0.08 for placebo; p=0.002

Phase 3 Trials: ORBIT-3 and -4 (1201 and 1202)

- Randomized, double-blind, placebo-controlled trials in patients with NCFB, history of 2 or more pulmonary exacerbations (PE) treated with antibacterials in previous 12 months, and positive sputum or deep throat culture for *P. aeruginosa*
- Randomization 2:1 to ciprofloxacin DI (189 mg once daily) or placebo (control liposomes and saline) in 28-day on/off cycles
- 48-week double-blind period, 28-day open-label extension
- Stratification by sex, number of exacerbations prior to screening, current smoking status

Phase 3 Trials: ORBIT-3 and -4

- Primary endpoint: time to first exacerbation by week 48
  - Exacerbation: change in 4 or more of 9 signs and symptoms concurrently
- First secondary endpoint: frequency of exacerbations by week 48
- Additional secondary endpoints
  - Frequency of severe exacerbations (requiring IV antibacterials and/or hospitalization)
  - Change from baseline to week 48 in Quality of Life – Bronchiectasis (QoL-B) Respiratory Symptoms Scale

Pulmonary Exacerbation Adjudication Committee (PEBAC) to review cases of discrepancies between protocol-defined criteria for PE and investigator's report

Phase 3 Trials: Statistical Considerations

- Hierarchical, step-down approach in each trial, separately
- If the primary endpoint of time to first PE at Week 48 was statistically significant at a 2-sided, 0.05 α level then:
  - Frequency of PEs tested at a 0.05, 2-sided α level
    - If significant, then a Holm-Bonferroni step-down procedure used to test the frequency of severe PEs and QoL-B Respiratory Symptoms Scale secondary endpoints

Re-Assessment of Outcome

- Unplanned data “re-review” after data base lock for both trials and after data were un-blinded and analyzed
  - Reason for re-review unclear
  - Programming errors affecting primary outcome status of 4 patients (2 in each trial)
- Applicant performed a “comprehensive audit of all eCRF entries for signs, symptoms or laboratory abnormalities as entered into the PE worksheets for all patients”
  - Led to blinded re-adjudication of 10 PEs (7 in ORBIT-3 and 3 in ORBIT-4) previously reviewed by the PEBAC
- Changes affecting total primary endpoint events

Primary Endpoint: Time to First PE

	ORBIT-3		ORBIT-4	
FA Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
Patients experiencing ≥ 1 PE	108 (59%)	54 (56.8%)	114 (55.3%)	64 (65.3%)
Diff (ciprofloxacin-Placebo)	**2.17%**		**-9.97%**	
Median time to first PE	214	136	230	158
Hazard Ratio	**0.99 [0.71, 1.38]**		**0.71 [0.52, 0.97]**	
Log-rank p-value	**0.974**		**0.032**	

Hazard model includes sex and prior PEs strata
Results based on data after re-review

Re-Assessment of Outcome

Identified programming errors and the re-adjudication of 10 PEs resulted in change in primary outcome for two patients in ORBIT-3 (both ciprofloxacin DI) and two patients in ORBIT-4 (both placebo)

Trial	Endpoint	Original data	Updated data
ORBIT-3	Patients with ≥ 1 PE	**106** (C), 54 (P)	**108** (C), 54 (P)
	P-value (Time to 1st PE)	0.826	0.974
ORBIT-4	Patients with ≥ 1 PE	114 (C), **62** (P)	114 (C), **64** (P)
	P-value (Time to 1st PE)	**0.058**	**0.032**

C=ciprofloxacin DI; P=placebo

Frequency of Exacerbations (Secondary Endpoint)

	ORBIT-3		ORBIT-4	
FA Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
Frequency of PEs	**199**	**124**	**202**	**144**
Mean	1.09 (1.20)	1.30 (1.53)	0.98 (1.16)	1.47 (1.60)
Range	0-5	0-5	0-6	0-8
IRR* (95% CI)	**0.85, (0.65, 1.12)**		**0.63, (0.49, 0.82)**	
p-value for IRR	0.253		0.0006	
Frequency of Severe PEs[#]	**41**	**27**	**28**	**29**
Mean	0.22 (0.56)	0.28 (0.72)	0.13 (0.42)	0.29 (0.58)
IRR* (95% CI)	0.80, (0.41, 1.51)		0.40, (0.22, 0.74)	
p-value for IRR	0.473		0.0027	

**Incidence Rate Ratio (IRR) obtained from a negative binomial regression model on total PEs including treatment, sex, number of prior PEs as factors, log(week) as an offset variable*

*Corrected P-value for testing of the frequency of severe PEs (based on Holm-Bonferroni) is 0.0027*2=0.0054<0.05*

[#]Defined as PEs requiring treatment w/IV antibiotics and/or hospitalization

Summary of Efficacy Results

- Unplanned re-review after data locking/unblinding led to changes in primary outcome
- ORBIT-3
  - Failed to demonstrate a difference between arms across all endpoints and analyses
  - Slightly more patients in the ciprofloxacin DI arm experiencing a PE compared to placebo
- ORBIT-4
  - Marginal effect on reducing time to first PE (based on re-review and re-adjudicated data)
  - Significant reduction in frequency of PEs and of severe PEs favoring ciprofloxacin DI
  - No demonstrated treatment effect on QoL-B Respiratory Symptoms Scale, pulmonary function, and duration of pulmonary exacerbations with ciprofloxacin DI
- Lack of clear explanation for discordant findings between trials
- No information about durability of efficacy findings over time

Safety Assessment

- 583 patients in pooled phase 3 safety population: 389 patients received at least one dose of ciprofloxacin DI, 193 patients received at least one dose of placebo liposomes and saline
- Similar rates of common treatment-emergent adverse events (AEs), AEs leading to withdrawal, serious AEs, and AEs leading to death in all groups
- Most treatment-emergent AEs appeared to be related to local effects of ciprofloxacin DI: dyspnea, bronchospasm, hemoptysis, cough, taste disorders
- Patients treated with ciprofloxacin DI more likely to have treatment-emergent ciprofloxacin-resistant *P. aeruginosa* cultured at any point post-baseline
- Unknown whether exposure beyond one year may lead to additional safety concerns, further increase in resistance to fluoroquinolones, or reduced treatment effect

Outline for the Day

- Presentations by the Applicant
- Presentations by the FDA
  - CDR LaRee Tracy, MA, PhD: Efficacy
  - Maria Allende, MD: Safety
  - Thomas Smith, MD: Summary
- Lunch
- Open public hearing
- Question for the committee

Question

- Has the applicant provided substantial evidence of the safety and efficacy of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation after starting treatment in non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa*?
  - If yes, please provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed? Please discuss appropriate endpoints, drug regimens and trial duration.


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Efficacy Evaluation: Ciprofloxacin Dispersion for Inhalation

Indication: Treatment of NCFBE with chronic lung infections with Pseudomonas aeruginosa

CDR LaRee Tracy, MA, PhD

Statistical Reviewer

Division of Biometrics IV

Office of Biostatistics, OTS, CDER, FDA

Outline

- Background
- Trial Design and Data Assessment
- Efficacy Findings
  - Time to first pulmonary exacerbation
  - Frequency of pulmonary exacerbations
  - Other secondary endpoints
- Sensitivity Analyses
- Issues/concerns
- Summary

Ciprofloxacin DI Clinical Development Program

Phase 2

- ORBIT-2 (trial 0902)
  - Randomized, double-blind, multicenter (NZ/Australia)
  - 6 month trial (28 days on/28 days off for ciprofloxacin DI (n=20) vs. placebo (n=22)
  - Primary Endpoint: Reduction in *P. aeruginosa* at Day 28, p=0.002
  - Secondary Endpoint: Time to First PE: Median days: 58 (placebo) and 134 days (ciprofloxacin DI)

Phase 3

- ORBIT-3 (trial 1201) (N=290 Randomized/278 Treated)
- ORBIT-4 (trial 1202) (N=308 Randomized/304 Treated)

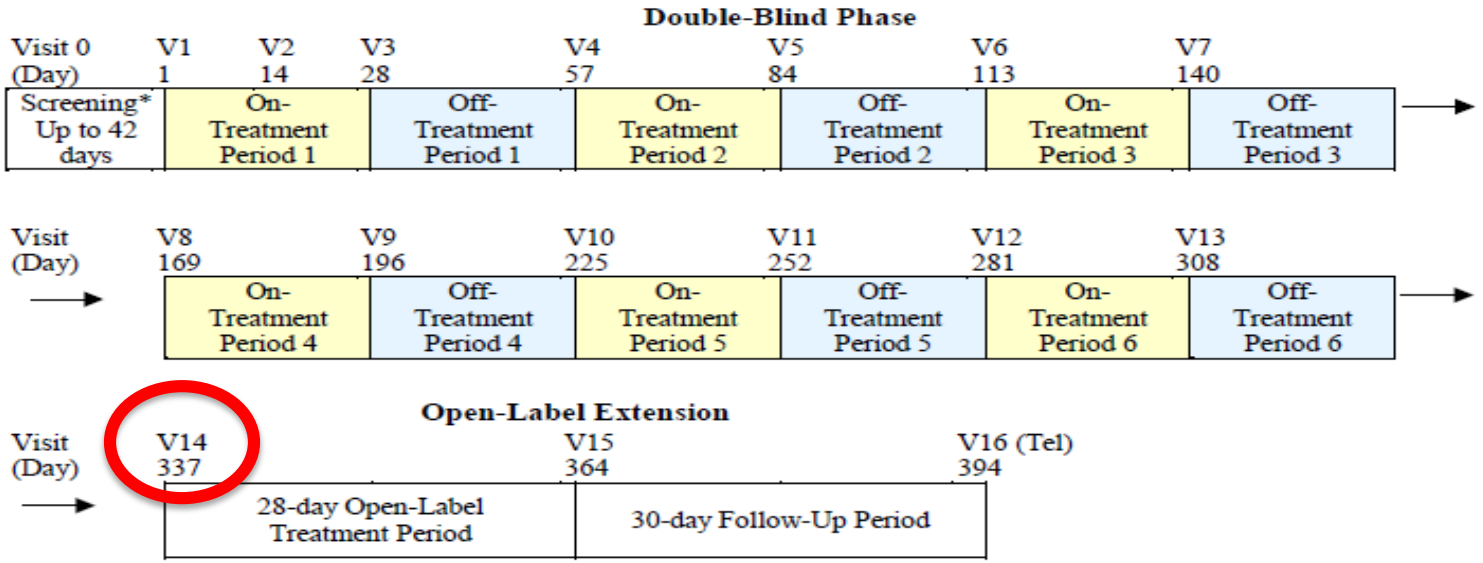
ORBIT-3 and ORBIT-4: Trial Design

- Identical designs (exception: ORBIT-3 includes a PK sub-study in extension phase)
- Phase 3, randomized, double-blind, placebo-control, multi-national
- Key Inclusion Criteria:
  - Males/females age ≥ 18 years of age, able to walk
  - Confirmed NCFB (per CT) showing bronchial wall dilatation w/ or w/o bronchial wall thickening
  - Documented history of ≥2 pulmonary exacerbations (PEs) treated w/antibiotics in past 12 mos
  - FEV1% predicted ≥ 25%
  - Positive sputum/deep-throat culture for *P. aeruginosa*

- Randomized **2:1** to ciprofloxacin DI or matching placebo (comprising control liposomes and saline)
  - Double-blind: 28 days on-treatment followed by 28 days off-treatment for 6 cycles (48 weeks/337 days duration)
  - Open-label extension: 28 days

- Stratification by current smoking status, sex and number of PEs prior to screening (2-3, 4-7, or >7)

ORBIT-3 and ORBIT-4: Trial Design



Tel = telephone call; V = Visit.
*Screening occurred between signing of the informed consent form and randomization.
Note: Each On-Treatment Period and Off-Treatment Period was 28 days in length.

Source: Trial Protocol

ORBIT-3 and ORBIT-4: Trial Endpoints

- **Primary Efficacy Endpoint-Time to First PE by Week 48**
  - *Exacerbation: change in 4 or more signs and symptoms* concurrently*
- First Secondary Endpoint-Frequency of Exacerbations at Week 48
  - *Exacerbation defined the same as above*
- *Other Secondary Endpoints*
  - *Frequency of severe PEs (severe defined as requiring treatment with IV antibiotics and/or hospitalization)*
  - *Change from baseline to Week 48 in Respiratory Symptoms Scale of the QoL-B Questionnaire*

- *Pulmonary Exacerbation Adjudication Committee (PEBAC) reviewed any cases of discrepancies between protocol-defined criteria for a PE and investigator's report*

*1) Change in sputum production, increased 2) dyspnea, 3) cough or 4) wheezing, 5) fever (≥ 38º C), 6) decreased exercise tolerance, malaise, fatigue or lethargy, 7) FEV1 or FVC decreased 10% from prior value, 8) radiographic changes, or 9) change in chest sounds

ORBIT-3 and ORBIT-4: Statistical Methods

Time to First PE

- Cox Proportional Hazards model stratified by sex and prior PEs (2-3, ≥4)
- Log-rank test statistic to compare survival between treatment arms

Frequency of Exacerbations

- Negative binomial regression including sex and prior PEs strata and log (time in trial) as an offset variable
- Same approach for analysis of frequency of severe PEs

QoL-B at Week 48

- Mixed effects model including sex and prior PE strata, baseline score, visit and treatment*visit as fixed effects, subject as repeated measure

Primary and secondary analysis in full analysis (FA) population including all randomized who received at least one dose of trial medication

ORBIT-3 and ORBIT-4: Statistical Testing Strategy

- Hierarchical, step-down approach in each trial, separately
- If the primary endpoint of time to first PE at Week 48 is statistically significant at a 2-sided, 0.05 alpha level then:
  - Frequency of PEs (secondary endpoint) tested at a 0.05, 2-sided alpha level
    - If significant, then a Holm-Bonferroni step-down procedure to test the frequency of severe PEs and QoL-B Respiratory Symptoms Scale secondary endpoints

➢ Pooling of secondary endpoint data for integrated efficacy ONLY if both trials achieve statistical significance on the primary endpoint

Re-Assessment of Outcome

- Unplanned data ‘re-review’ after data base lock for both trials and after data were un-blinded and analyzed
  - Reason for re-review unclear
  - Programming errors affecting primary outcome status of 4 patients (2 in each trial)
- Applicant performed a ‘comprehensive audit of all eCRF entries for signs, symptoms or laboratory abnormalities as entered into the PE worksheets for all patients’
  - Led to blinded re-adjudication of 10 PEs (7 in ORBIT-3 and 3 in ORBIT-4) previously reviewed by the PEBAC
- Changes affecting total primary endpoint events
  - results before and after changes presented on a subsequent slide

Patient Disposition

	ORBIT-3		ORBIT-4	
Disposition, n (%)	ciprofloxacin DI	Placebo	ciprofloxacin DI	Placebo
Randomized	193	97	207	101
Did not receive drug	10 (5.2)	2 (2.1)	1 (0.5)	3 (3.0)
Full Analysis Population	**183 (94.8)**	**95 (97.9)**	**206 (99.5)**	**98 (97.0)**
Per Protocol Population	145 (75.1)	78 (80.5)	176 (85.0)	76 (75.2)
Died*	5 (2.7)	3 (3.2)	2 (1)	4 (4.1)
Premature Trial Discontinuation*	41 (22.4)	18 (18.9)	28 (13.6)	17 (17.3)
Adverse Event	**16 (8.7)**	**3 (3.1)**	**5 (2.4)**	**4 (4.1)**
Lost to Follow-Up	3 (1.6)	1 (1.0)	3 (1.5)	0
Patient Withdrawal	***14 (7.6)***	***11 (11.6)***	***13 (6.3)***	***11 (11.2)***
Lack of Efficacy	3 (1.6)	0	1 (0.5)	0
Investigator Decision	3 (1.6)	1 (1.0)	3 (1.5)	1 (1.0)
Protocol Deviation	2 (1.1)	1 (1.0)	1 (0.5)	1 (0.5)
Other	0	1 (1.0)	2 (1.0)	0
Completed DB Period*	142 (77.6)	77 (81.1)	178 (86.4)	81 (82.7)

*Percentages are of FA population

Patient Characteristics

	ORBIT-3		ORBIT-4	
Full Analysis Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
Female	127 (69.4)	67 (70.5)	134 (65.0)	63 (64.3)
Age Mean (sd)	64.3 (13.6)	66.7 (10.7)	63.3 (13.4)	64.2 (12.6)
Age ≥65 years	108 (59.0)	61 (64.2)	110 (53.4)	55 (56.1)
Prior PEs Mean (SD) [range]	2.8 (1.3) [2-10]	2.8 (1.2) [1-6]	2.8 (1.2) [2-11]	3.0 (1.6) [1-12]
Quit Smoking ≥ 1 year	56 (30.6)	32 (33.7)	55 (26.7)	25 (25.5)
Current Smoker	**3 (1.6)**	**1 (1.0)**	**2 (0.1)**	**0**
FEV1% Predicted Mean (SD)	57.3 (21.9)	57.4 (20.2)	62.5 (22.2)	59.8 (20.8)
FVC% Predicted Mean (SD)	70.1 (20.2)	68.9 (18.4)	74.3 (19.4)	74.1 (19.1)
BL Macrolide Use	**43 (23.5)**	**13 (13.7)**	**34 (16.5)**	**24 (24.5)**
Race				
White	161 (88.9)	89 (93.7)	168 (84.4)	82 (88.2)
Asian	15 (8.3)	4 (4.2)	11 (5.5)	4 (4.3)
Region				
Western Europe	59 (32.2)	31 (32.6)	65 (31.5)	43 (43.9)
USA/Canada	44 (24.0)	15 (15.8)	34 (16.5)	12 (12.2)
Other Region*	16 (8.7)	9 (9.5)	26 (12.6)	9 (9.2)
Central/Eastern Europe	**21 (11.5)**	**13 (13.7)**	**53 (25.7)**	**20 (20.4)**
Australia/NZ	**43 (23.5)**	**27 (28.4)**	**28 (13.6)**	**14 (14.3)**

*other: ORBIT-3 includes S. Korea (n=2), Taiwan (n=9) and S. Africa (n=14); ORBIT-4 includes S. Korea (n=14) and Peru (n=21)

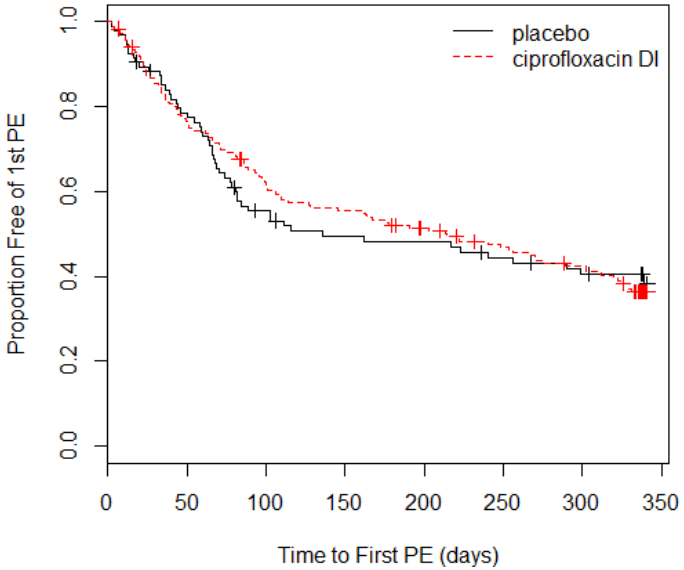
Primary Endpoint: Time to First PE

	ORBIT-3		ORBIT-4	
FA Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
Patients experiencing ≥ 1 PE	108 (59.0%)	54 (56.8%)	114 (55.3%)	64 (65.3%)
Diff (ciprofloxacin-Placebo)	**2.17%**		**-9.97%**	
Median time to first PE	214	136	230	158
Hazard Ratio	**0.99 [0.71, 1.38]**		**0.71 [0.52, 0.97]**	
Log-rank p-value	**0.974**		**0.032**	

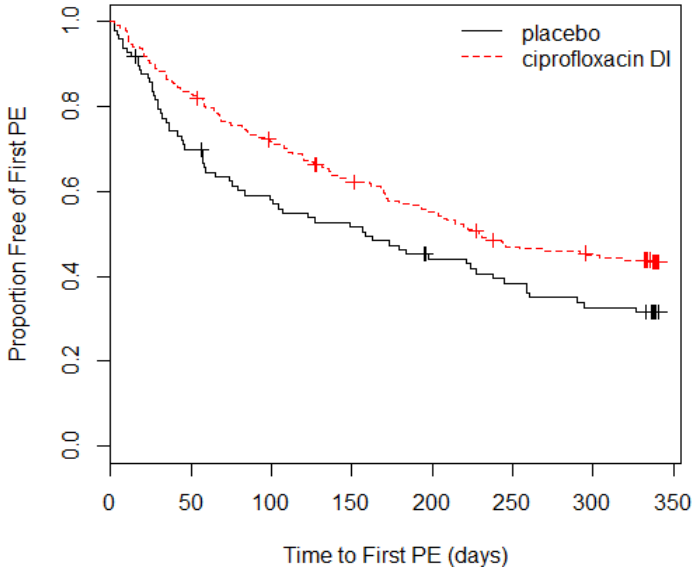
Hazard model includes sex and prior PEs strata

Time to First PE (Primary Endpoint)

ORBIT-3



ORBIT-4



Re-Assessment of Outcome

Identified programming errors and the re-adjudication of 10 PEs resulted in change in primary outcome for two patients in ORBIT-3 (both ciprofloxacin DI) and two patients in ORBIT-4 (both placebo)

Trial	Endpoint	Original data	Updated data
ORBIT-3	Patients with ≥ 1 PE	**106** (C), 54 (PC)	**108** (C), 54 (PC)
	Hazard Ratio	0.97	0.99
	P-value (Time to 1st PE)	**0.826**	**0.974**
ORBIT-4	Patients with ≥ 1 PE	114 (C), **62** (PC)	114 (C), **64** (PC)
	Hazard Ratio	0.74	0.71
	P-value (Time to 1st PE)	**0.058**	**0.032**

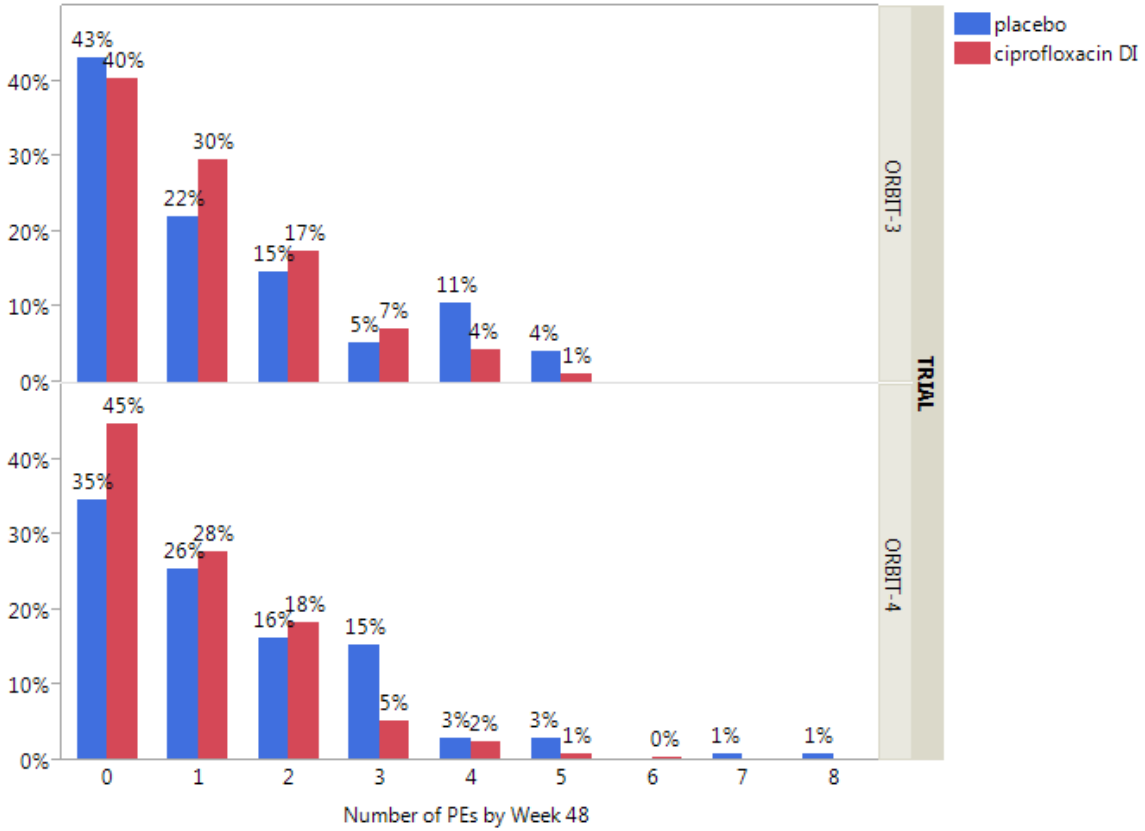
C=ciprofloxacin DI; P=placebo

Frequency of Exacerbations (Secondary Endpoint)

	ORBIT-3		ORBIT-4	
FA Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
Frequency of PEs	**199**	**124**	**202**	**144**
Mean	1.09 (1.20)	1.30 (1.53)	0.98 (1.16)	1.47 (1.60)
Range	0-5	0-5	0-6	0-8
IRR* (95% CI)	0.85, (0.65, 1.12)		**0.63, (0.49, 0.82)**	
p-value for IRR	0.253		**0.0006**	
Frequency of Severe PEs#	**41**	**27**	**28**	**29**
Mean	0.22 (0.56)	0.28 (0.72)	0.13 (0.42)	0.29 (0.58)
IRR* (95% CI)	0.80, (0.41, 1.51)		**0.40, (0.22, 0.74)**	
p-value for IRR	0.473		0.0027^	

**Incidence Rate Ratio (IRR) from negative binomial model including treatment, sex, prior PEs, log(week) as an offset*
#PEs requiring treatment w/IV antibiotics and/or hospitalization; ^Corrected P-value =0.0014 (based on Holm-Bonferroni 0.0027/2)<0.05

Distribution of Patients by Frequency of PEs



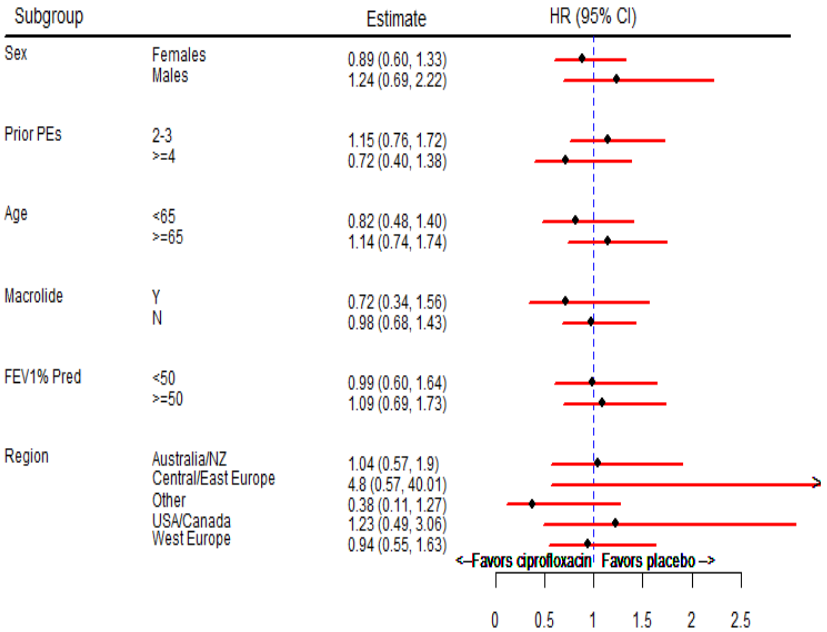
Other Secondary Endpoints

	ORBIT-3		ORBIT-4	
FA Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
QoL-B Respiratory Symptoms				
n	142	77	183	82
Mean Score	57.22 (19.86)	58.85 (16.80)	64.47 (19.86)	63.88 (19.67)
LS Mean (SE)*	2.09 (1.31)	3.71 (1.73)	7.71 (1.21)	6.86 (1.69)
Difference (ciprofloxacin-placebo) (sd)	**-1.62 (2.06)**		**0.84 (1.95)**	
95% CI	[-5.64, 2.43]		[-2.98, 4.66]	
p-value	**0.43**		**0.66**	
FEV1% Predicted				
n	133	70	163	77
Mean % Change from BL	-1.48 (13.4)	-3.52 (11.78)	-2.05 (12.46)	-2.67 (11.40)
LS Mean Diff (ciprofloxacin-placebo)	1.74 (1.90), p=0.36		0.66 (1.68), p=0.69	

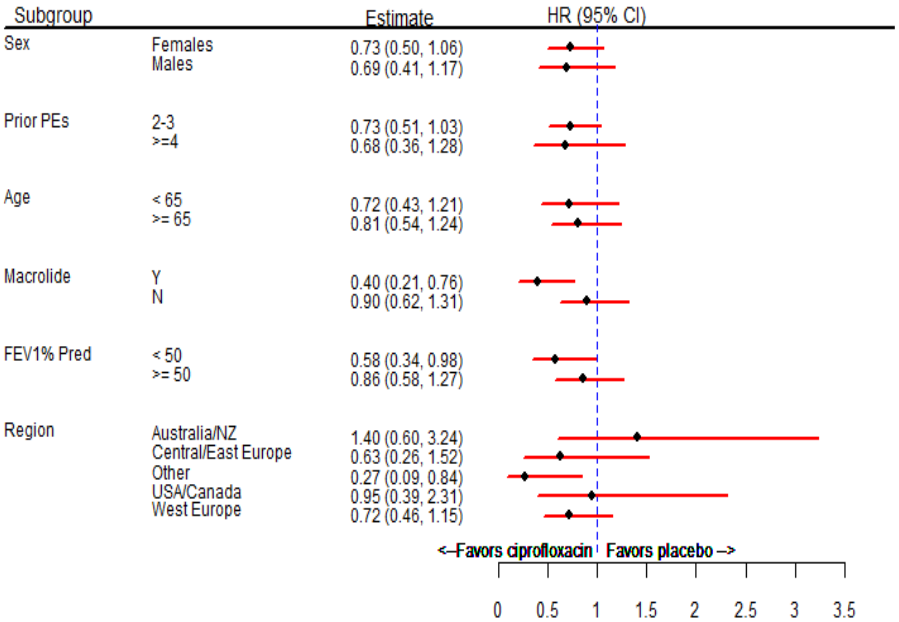
***Model includes treatment and visit and treatment by visit fixed effects, subject as the random effect and covariates of baseline value, sex and prior PEs
QOL-B results include questionnaire question on sputum color

Time to First PE by Subgroup

ORBIT-3



ORBIT-4



Sensitivity Analyses: Baseline Macrolide Use

	ORBIT-3		ORBIT-4	
FA Population	**ciprofloxacin DI (n=183)**	**Placebo (n=95)**	**ciprofloxacin DI (n=206)**	**Placebo (n=98)**
Time to First PE				
Hazard Ratio	0.93 (0.66, 1.30)		0.74 (0.54, 1.01)	
Log-rank p-value	0.731		0.057	
Frequency of PEs				
IRR (95% CI)	0.83 (0.63, 1.09)		0.66 (0.51, 0.86)	
p-value for IRR	0.173		0.002	

Models include sex, prior PEs and baseline macrolide use (y/n) strata. Frequency of PE model includes log (time in trial) as an offset variable.

Additional Sensitivity Analyses

Stratifying by sex and number of prior PEs (numeric)

Time to First PE

- ORBIT-3: HR and 95% CI: 0.93 (0.67, 1.31), p=0.702
- ORBIT-4: HR and 95% CI: 0.73 (0.52, 1.01), p=0.053

Frequency of PEs

- ORBIT-3: IRR and 95% CI: 0.84 (0.64, 1.10), p=0.206
- ORBIT-4: IRR and 95% CI: 0.64 (0.50, 0.83), p=0.0008

Issues and Limitations

- Primary Endpoint: Time to first PE
  - Ignores subsequent exacerbations and therefore not a full characterization of disease-related events
- Secondary Endpoint: Frequency of PEs
  - Captures all events; however, it does not account for duration of exacerbations to accurately model at-risk intervals for each patient
- Long-term efficacy of chronic ciprofloxacin unknown
  - Limited trial duration of 48 weeks treatment may not fully predict long-term effect for chronic disease

Summary

- Unplanned re-review after data locking/unblinding led to changes in primary outcome

- **ORBIT-3**
  - More patients in ciprofloxacin DI prematurely withdrew from trial compared to placebo
  - Failed to demonstrate a difference between arms across all endpoints and analyses
  - Slightly more patients in the ciprofloxacin DI arm experiencing a PE compared to placebo

- **ORBIT-4**
  - More placebo patients compared to ciprofloxacin DI prematurely withdrew from trial
  - Marginal effect on reducing time to first PE (based on re-review and re-adjudicated data)
  - Significant reduction in frequency of PEs and of severe PEs favoring ciprofloxacin DI
  - No demonstrated treatment effect on QoL-B Respiratory Symptom Scale, pulmonary function and duration of pulmonary exacerbations with ciprofloxacin DI

- Lack of clear explanation for discordant findings between trials

- Trials too short to understand if treatment effect will persist over time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Presentation of Clinical Safety

Maria Allende, MD
Medical Officer
Division of Anti-Infective Products

NDA 210693
Antimicrobial Drugs Advisory Committee
January 11, 2018

Outline

- Safety assessments of to-be-marketed product:
  - Phase 2
  - Phase 3
- Differences noted in the adverse events profile between treatment and placebo arms across the two Phase 3 trials
- Spirometry assessments for safety
- Resistance of *P. aeruginosa* to ciprofloxacin during follow-up
- Conclusions

Goal of the Safety Review

- Systemic and local adverse events related to the inhaled route of administration
- Difficulties in assessment of causality: overlap of adverse events and disease outcomes, comorbidities and concomitant medications

Safety Database

- One Phase 2 study, 1:1 randomization (N=42)
- Two Phase 3 studies, 2:1 randomization (N=582)
- Total N=624 randomized, of whom:
    - N=409 received at least one dose of ciprofloxacin DI
    - N=215 received at least one dose of placebo

Phase 1 and 2 Safety

- Phase 1 and Phase 2a studies
  - 15 subjects treated with ciprofloxacin DI prototype formulations (9 healthy subjects and 6 NCFBE) crossover study
  - 20 healthy subjects treated with the liposomal formulation (CFI)
  - 36 NCFBE patients treated with CFI for 28 days
- Phase 2 study
  - 42 participants (20 treated and 22 placebo controls)
  - Ciprofloxacin DI and placebo formulations to be used in Phase 3 trials
  - Primary endpoint: Microbiological efficacy
  - Three 28-days On and three 28-days Off cycles, total of 6 months

Phase 2 Safety: ORBIT-2

- No deaths were reported. A total of 3/20 (15%) and 3/22 (13.6%) patients in treatment and placebo arms, respectively, experienced serious adverse events (SAEs) of “lung disorder” (pulmonary exacerbations and respiratory infections).

- “Lung disorder,” wheezing, hemoptysis, dyspnea and abnormal product taste were most common adverse events (AEs), and occurred at comparable rates in the placebo and treatment arms

Phase 3 Safety

- Two Phase 3 trials: ORBIT-3 and 4
  - 582 patients included in the pooled Phase 3 safety population
    - 389 patients received at least one dose of ciprofloxacin DI
    - 193 patients received at least one dose of placebo

Summary of Phase 3 Safety

	ORBIT-3		ORBIT-4		Pooled Studies	
	Ciprofloxacin DI (N=183)	Placebo (N=95)	Ciprofloxacin DI (N=206)	Placebo (N=98)	Ciprofloxacin DI (N=389)	Placebo (N=193)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Patients with any TEAE	164 (89.6)	87 (91.6)	179 (86.9)	95 (96.9)	343 (88.2)	182 (94.3)
Patients with severe TEAE	46 (25.1)	20 (21.1)	39 (18.9)	27 (27.6)	85 (21.9)	47 (24.4)
Patients with treatment emergent SAE	56 (30.6)	24 (25.6)	35 (17.0)	28 (28.6)	91 (23.4)	52 (26.9)
Patients with TEAE leading to death	5 (2.7)	3 (3.2)	2 (1.0)	4 (4.1)	7 (1.8)	7 (3.6)
Patients with TEAE leading to permanent discontinuation	24 (13.1)	8 (8.4)	10 (4.9)	7 (7.1)	34 (8.7)	15 (7.8)

Note: Frequency data are based on the number of subjects with the event.

Deaths in Phase 3 Trials

Trial	ciprofloxacin DI	Placebo
Pooled Studies	**7/389 (1.8%)**	**7/193 (3.6%)**
ORBIT-3	**n= 5 (2.7%)**	**n= 3 (3.2%)**
	Pneumonia, n=1 Respiratory failure, n=1 Unresponsive, n=1 Loss of consciousness, n=1 Thalamus hemorrhage, n=1	Pneumonia, n=1 Respiratory failure, n=1 Pancreatic carcinoma, n=1
ORBIT-4	**n= 2 (1.0%)**	**n= 4 (4.1%)**
	Bronchopneumonia, n=1 Sudden death, n=1	Respiratory failure, n=3 Bronchiectasis, n=1

Selected SAEs in ≥2 Patients in the Ciprofloxacin DI Arm in Phase 3 Trials

	ORBIT-3		ORBIT-4		Pooled Studies	
Adverse Event	Ciprofloxacin DI N (%)	Placebo N (%)	Ciprofloxacin DI N (%)	Placebo N (%)	Ciprofloxacin DI N (%)	Placebo N (%)
Dyspnea	11 (6.0)	8 (8.4)	6 (2.9)	5 (5.1)	17 (4.4)	13 (6.7)
Pneumonia*	8 (4.3)	7 (7.3)	8 (3.9)	0 (0)	16 (4.1)	7 (3.6)
Hemoptysis	7 (3.8)	1 (1.1)	2 (1.0)	1 (1.0)	**9 (2.3)**	**2 (1.0)**
Cough	5 (2.7)	1 (1.1)	1 (0.5)	1 (1.0)	6 (1.5)	2 (1.0)
Bronchospasm*	4 (2.2)	2 (2.1)	3 (1.5)	1 (1.0)	7 (1.8)	3 (1.6)
Respiratory failure*	4 (2.2)	0 (0)	6 (2.9)	4 (4.1)	10 (2.6)	4 (2.1)
Hypoxia	2 (1.1)	0 (0)	0 (0)	0 (0)	2 (0.5)	0 (0)

* Pneumonia includes *"pneumonia," "pneumonia bacterial,"* and *"pneumonia viral," and "respiratory syncytial virus infection;"* * Bronchospasm includes "*bronchospasm,*" *"obstructive airways disorder," "wheezing," and "asthma;"*
* Respiratory failure includes "*respiratory failure*" and "*acute respiratory failure*"

Phase 3 TEAEs Leading to Premature Treatment Discontinuation - Double Blind Phase

Type of TEAE leading to premature discontinuation of study drug	ORBIT-3		ORBIT-4		Pooled studies	
	Ciprofloxacin DI (N=183) N (%)	Placebo (N=95) N (%)	Ciprofloxacin DI (N=206) N (%)	Placebo (N=98) N (%)	Ciprofloxacin DI (N=389) N (%)	Placebo (N=193) N (%)
Any TEAE	24 (13.1%)	8 (8.4%)	10 (4.9%)	7 (7.1%)	34 (8.7%)	15 (7.8%)
Any SAE*	5 (2.7%)	2 (2.1%)	2 (1.0%)	2 (2.0%)	7 (1.8%)	4 (2.1%)

**SAEs are a subset of "Any TEAE", however, percentages of SAEs are calculated using the total N of each arm (not the N of subjects with any TEAE)*

Most frequent SAEs leading to drug discontinuation were Respiratory events and included: *Bronchospasm, Dyspnea, Hemoptysis, Hypoxia, Acute Respiratory Failure, Infective Exacerbation of COPD*

Source: ADSL and ADAE, AEACN, selecting action taken with study drug "withdrawn" , Epoch Double Blind phase

TEAEs of Special Interest

	ORBIT-3		ORBIT-4		Pooled Studies	
Adverse Event	Ciprofloxacin Di	Placebo	Ciprofloxacin DI	Placebo	Ciprofloxacin DI	Placebo
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cough*	115 (63)	55 (58)	138 (67)	71 (73)	253 (65)	126 (65)
Dyspnea	102 (56)	48 (51)	107 (52)	55 (56)	209 (54)	103 (53)
Bronchospasm*	96 (53)	45 (47)	120 (58)	60 (61)	216 (56)	105 (54)
Wheezing	69 (38)	34 (36)	83 (40)	49 (50)	152 (39)	83 (43)
Forced expiratory volume decreased	56 (31)	18 (19)	66 (32)	31 (32)	122 (31)	49 (25)
Forced vital capacity decreased	31 (17)	13 (14)	45 (22)	23 (24)	76 (20)	36 (19)
Hemoptysis	30 (16)	9 (10)	27 (13)	18 (18)	57 (15)	27 (14)
Pneumonia*	13 (7)	8 (8)	9 (4)	0 (0)	22 (6)	8 (4)
Chest pain	10 (5)	5 (5)	11 (5)	4 (4)	21 (5)	9 (5)
Upper respiratory tract infection	10 (5)	1 (1)	9 (4)	1 (1)	19 (5)	2 (1)
Epistaxis	2 (1)	0 (0)	5 (2)	0 (0)	7 (2)	0 (0)
Hypoxia	4 (2)	0 (0)	1 (0.5)	0 (0)	5 (1)	0 (0)
Oxygen saturation decreased	4 (2)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)

**Cough*: *cough, cough productive, upper airways cough syndrome*
***Bronchospasm**: wheezing, forced expiratory volume decreased, bronchospasm, asthma, asthmatic crisis, prolonged expiration, obstructive airways disorder. *Pneumonia: pneumonia, pneumonia bacterial, pneumonia viral*

TEAEs Most Likely Due to Inhaled Route of Administration in Phase 3 Trials

- It is plausible that the inhaled drug caused irritation of the respiratory tract resulting in these AEs:
  - Cough
  - Hemoptysis
  - Bronchospasm

Serial Spirometry – Percent of Patients with ≥15% Decrease in FEV_1 % Predicted*

- Assessments for safety were done at 4 timepoints: before treatment and at 15, 30 and 90 minutes at Visits 1 and 8

At any timepoint:	Ciprofloxacin DI, N (%)	Placebo N(%)
Visit 1	32 (8.6)	11 (5.9)
Visit 8	18 (5.8)	4 (2.6)

*: Pooled studies data are presented. The same trends were observed in each individual study

Evaluation of Fluoroquinolone Class Effects

- Systemic exposure to ciprofloxacin DI is 10 fold lower than following orally or intravenously administered ciprofloxacin at approved doses
- Confounding factor: approximately 50% of patients received oral or IV ciprofloxacin during the study
- Adverse events associated with fluoroquinolone class effects, such as tendon rupture, musculoskeletal pain, arthralgia and peripheral neuropathy were not higher in the treatment arm as compared to the placebo arm

Evaluation of *P. aeruginosa* Resistance to Ciprofloxacin

- Sputum cultures were to be taken from all patients at baseline and each follow-up visit
  - Distribution of *P. aeruginosa* isolates by treatment arm, at baseline and after treatment :
    - Sensitive (MIC <1 mcg/mL)
    - Intermediate (2 mcg/mL) and
    - Resistant (MIC ≥4 mcg/mL)
  - Number of patients who acquired resistant *P. aeruginosa* isolates during follow-up, by treatment arm
  - Effect of exposure to treatment cycles: highest ciprofloxacin MIC isolates by treatment group and study visits

Percentage of Isolates by MIC Category (ORBIT-3 and -4)

Visit	Ciprofloxacin DI %			Placebo %		
	Susceptible ≤0.25 -1 mcg/mL	Intermediate 2 mcg/mL	Resistant ≥ 4 mcg/mL	Susceptible ≤0.25 -1 mcg/mL	Intermediate 2 mcg/mL	Resistant ≥ 4 mcg/mL
	ORBIT 3					
1	64.6	14.1	21.2	69.6	12.7	17.7
12	47.8	18.7	33.6	63.7	10.3	25.9
13	33.9	22.9	43.1	72.7	16.7	10.6
14	47.7	20.8	31.5	74.7	12.7	12.7
	ORBIT 4					
1	74.3	10.5	15.2	71.5	9.8	18.7
12	48.6	19.3	32.1	69.1	16.0	14.8
13	33.9	20.0	46.1	79.7	5.1	15.2
14	53.2	13.7	33.1	68.5	16.4	15.1

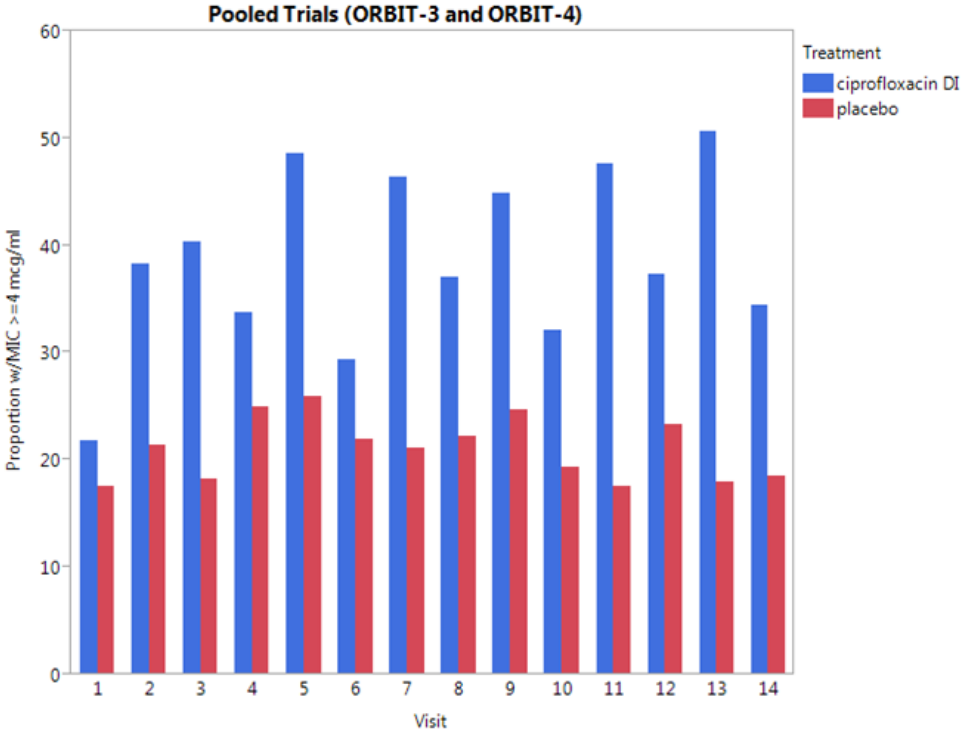
Visit 1: Baseline; Visit 12: Start of 6th Treatment cycle; Visit 13: End of 6th Treatment cycle; Visit 14: End of 6th off-cycle

Proportion of Patients with Ciprofloxacin-Resistant *P. aeruginosa* Isolates (MIC >=4 mcg/mL)

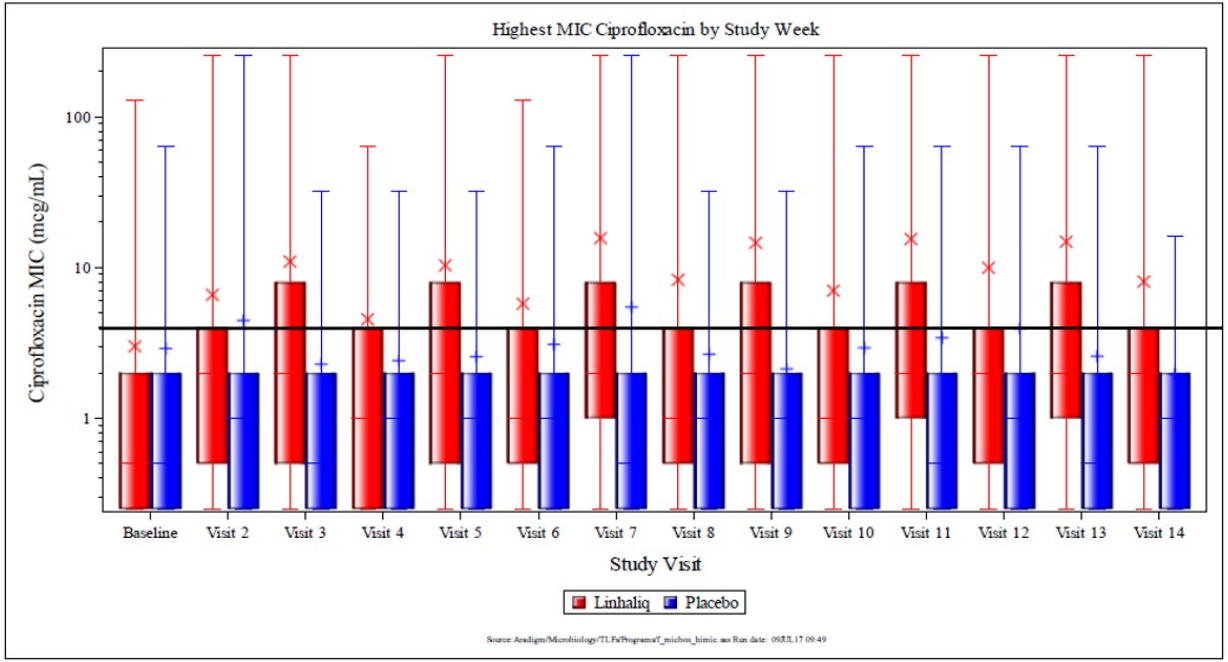
Visit	ORBIT-3		ORBIT-4		Pooled Studies	
	Ciprofloxacin DI	Placebo	Ciprofloxacin DI	Placebo	Ciprofloxacin DI	Placebo
1	35/136 (25.7)	13/95 (13.7)	29/158 (18.3)	18/81 (22.2)	64/294 (21.8)	31/176 (17.6)
12	34/87 (39.1)	11/41 (26.8)	36/100 (36)	11/53 (20.7)	70/187 (37.4)	22/94 (23.4)
13	36/74 (48.6)	7/46 (15.2)	48/92 (52.2)	11/54 (20.4)	84/166 (50.6)	18/100 (18)
14	31/90 (34.4)	7/47 (14.9)	35/101 (34.6)	11/50 (22)	66/191 (34.5)	18/97 (18.5)

Visit 1: Baseline; Visit 12: Start of 6th Treatment cycle; Visit 13: End of 6th Treatment cycle; Visit 14: End of 6th off-cycle

Proportion of Patients with *P. aeruginosa* Ciprofloxacin-Resistant Isolates (MIC ≥4 mcg/mL) – All Visits



Box and Whisker Plots of Ciprofloxacin MICs of Highest Ciprofloxacin MIC *P. aeruginosa* Isolates by Treatment Group and Study Visit, Pooled Studies ORBIT-3 and ORBIT-4 (FA Population)



Note: Includes data from one isolate per subject per visit, based on the highest MIC result at a visit.
Source: Appendix Figure 3.1

Safety Conclusions

- Although differences were observed in the safety profile between ORBIT-3 and -4, most were balanced in the pooled analyses
- A higher proportion of patients with worsening of lung function (FEV_1 % predicted) was observed with study drug administration
- Increased ciprofloxacin resistance from baseline to follow-up seen in treatment arm compared to placebo
- Unknown whether exposure beyond one year may lead to additional safety concerns, increased resistance to fluoroquinolones, or result in reduced treatment effect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Summary Presentation

Thomas Smith, MD
Clinical Team Leader
Division of Anti-Infective Products

NCFB Clinical Trials

- There are no approved therapies for prevention or management of NCFB exacerbations.
- We recognize the need for safe and effective therapies for patients with NCFB.
- Studies of other inhaled antibacterial drugs (tobramycin, gentamicin, aztreonam, colistin, and ciprofloxacin) for the prevention of NCFB exacerbations have yielded mixed results, and none are approved for this indication.*
- There are uncertainties regarding the duration of treatment, frequency of administration, and appropriate endpoints to use in clinical trials of NCFB.

*Publications referenced in FDA briefing document

Overall Observations

- Unplanned re-review after data locking/unblinding led to changes in primary outcome
- ORBIT-3
  - Failed to demonstrate a difference between arms across all endpoints and analyses
  - Slightly more patients in the ciprofloxacin DI arm experiencing a PE compared to placebo
- ORBIT-4
  - Marginal effect on reducing time to first PE (based on re-review and re-adjudicated data)
  - Significant reduction in frequency of PEs and of severe PEs favoring ciprofloxacin DI
  - No demonstrated treatment effect on QoL-B Respiratory Symptoms Scale, pulmonary function, and duration of pulmonary exacerbations with ciprofloxacin DI
- Lack of clear explanation for discordant findings between trials
- Similar rates of common treatment-emergent adverse events (AEs), AEs leading to withdrawal, serious AEs, and AEs leading to death in all groups
- Patients treated with ciprofloxacin DI more likely to have treatment-emergent ciprofloxacin-resistant *P. aeruginosa* cultured at any point post-baseline

Uncertainties

- Clinical relevance of the observed treatment effects when risks such as adverse reactions and development of resistance are considered
- Durability of efficacy and safety findings beyond one year (e.g., development of resistance)
- Long-term use of inhaled ciprofloxacin could limit the utility of systemic fluoroquinolones for treatment of severe bacterial exacerbations and pneumonia in NCFB patients

Question

- Has the applicant provided substantial evidence of the safety and efficacy of ciprofloxacin dispersion for inhalation in delaying the time to first exacerbation after starting treatment in non-cystic fibrosis bronchiectasis patients with chronic lung infections with *Pseudomonas aeruginosa*?
  - If yes, please provide any recommendations concerning labeling.
  - If no, what additional studies/analyses are needed? Please discuss appropriate endpoints, drug regimens and trial duration.