2 SYNOPSIS

Name of Sponsor/Company: Mpex Pharmaceuticals, Inc. **Name of Finished Product:** Levofloxacin Inhalation Solution **Name of Active Ingredient:** Levofloxacin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*

Title of Study: A Phase 3, Open-label, Randomized Trial to Evaluate the Safety and Efficacy of MP-376 Inhalation Solution (Aeroquin™) Versus Tobramycin Inhalation Solution (TIS) in Stable Cystic Fibrosis Patients

Principal Investigators and Study Centers:
Coordinating Investigator: [redacted], Medical University of South Carolina.
The 95 Principal Investigators (95 sites) in the United States, 11 Principal Investigators (11 sites) in Germany, 6 Principal Investigators (6 sites) each in France and the United Kingdom (UK), 3 Principal Investigators (3 sites) in Ireland, and 4 Principal Investigators (4 sites) in Israel are identified in [redacted]

Publication (Reference): None

Study Period (Years): 27 January 2011 (first patient screened) to 01 August 2012 (last study visit)

Phase of Development: 3

Objectives:

To compare the safety of MP-376 and TIS when administered over multiple cycles.

To compare the efficacy of MP-376 and TIS administered over 28 days.

To explore the comparative efficacy of MP-376 and TIS when administered over multiple cycles.

Methodology: This was a multinational, multi-center, randomized, open-label, multi-cycle, active-controlled, parallel-group study in stable cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa (P. aeruginosa)* lung infection at least 12 years of age and weighing at least 30 kilograms (kg) to evaluate the comparative safety of MP-376 and TIS over 3 consecutive 56-day cycles (28 days on treatment and 28 days off treatment). Efficacy data for MP-376 and TIS at the end of the first 28-day treatment period were also compared, as well as evaluated over multiple treatment cycles. Randomization was performed via an automated interactive voice response system (IVRS) at Visit 1 (Day 1) and was stratified by geographic region (US, non-US), age (12 to 18 years, > 18 years), and forced expiratory volume in 1 second (FEV_1) percent predicted (< 55%, ≥ 55%) values at Screening (based on Hankinson/National Health and Nutrition Examination Survey [NHANES] III criteria).

MP-376 was administered by inhalation using a modified configuration of the PARI eFlow® nebulizer (hereafter referred to as the MP-376-customized PARI eFlow® nebulizer) and TIS was administered using the PARI LC® PLUS nebulizer with compressor or via another nebulizer compatible with country-specific labeling. Patients were to remain off of any other antipseudomonal antimicrobials other than Study Drug (MP-376 or TIS) for the duration of the

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study unless they met the protocol-defined definition of an exacerbation or unless antipseudomonal antimicrobials were deemed necessary for safety reasons by the Investigator.

The screening period was up to 14 days and included evaluations of entry criteria, demographics, medical history, safety assessments, and a sputum sample collection for microbiology culture. Patients could be rescreened for entry into the study (based on FEV_1 results, *P. aeruginosa* sputum sample results, or clinical stability), either within the 14-day screening period or subsequently with permission from the Sponsor or designee.

At Visit 1/Day 1, eligibility was confirmed, patients were randomized, protocol-defined assessments were performed, and serum and sputum samples were taken for microbiology. Patients were instructed on the procedure for self-administration of Study Drug and site staff observed the administration of the first dose. Patients self-administered Study Drug twice daily (BID) approximately 8 to 12 hours apart for the remainder of the first 28-day treatment period. Patients returned to the study site for Visit 2 on Day 28, when safety and efficacy assessments were repeated. A site staff member observed the patient self-administer the last Study Drug dose of the first treatment period. Pre-dose serum samples and post-dose serum and sputum samples were collected for pharmacokinetic (PK) analysis for patients receiving MP-376.

Patients did not administer Study Drug for the next 28 days and returned to the study site for Visit 3 on Day 56, when safety and efficacy assessments were repeated and a site staff member observed the patient self-administer the first Study Drug dose of the second treatment period. The cycle was then repeated, with the patient returning to the site on Day 84 (Visit 4, end of the second treatment period), Day 112 (Visit 5, start of the third treatment period), Day 140 (Visit 6, end of the third treatment period), and Day 168 (Visit 7, Final/Early Termination [ET] visit).

Patients were given the option of continuing after this core phase in an extension phase in which they would receive MP-376 (regardless of whether they had received MP-376 or TIS previously) for an additional three 56-day cycles (28 days on treatment and 28 days off treatment). The extension phase is the subject of another clinical study report and is not described further in this report.

Patients who prematurely discontinued Study Drug after the first dose were encouraged to continue to attend subsequent study visits and all study procedures were performed except for sample collections for PK analysis.

Number of Patients (Planned and Analyzed):
Planned enrollment: 267

Enrolled, received study medication, and analyzed: 282 patients were randomized, 272 received at least 1 dose of Study Drug and were included in the Safety population (182 MP-376, 90 TIS). The primary efficacy analysis was based on the Intent-to-Treat (ITT) population of all randomized patients, regardless of whether treatment was received or what

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treatment the patient actually received (189 MP-376, 93 TIS).

Additional supportive efficacy analyses were performed using the Day 28 Efficacy Evaluable (EE28) population of all randomized patients without major protocol violations who received at least 80% of planned Study Drug doses during the first 28-day treatment period (158 MP-376, 77 TIS) and the Day 140 Efficacy Evaluable (EE140) population of all randomized patients without major protocol violations who received at least 80% of planned Study Drug doses over the three 28-day treatment periods (122 MP-376, 55 TIS). The PK data were analyzed for the PK population (171 MP-376-treated patients), defined as all patients who received at least 1 dose of MP-376 and had at least 1 PK sample collected.

Diagnosis and Main Criteria for Inclusion: Eligible patients were at least 12 years of age, weighed at least 30 kg (66 pounds), and had a diagnosis of CF. Documentation of a CF diagnosis was evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria: sweat chloride $\geq$ 60 mEq/L by quantitative pilocarpine iontophoresis test, 2 well-characterized mutations in the CF transmembrane conductive regulator gene, and/or abnormal nasal potential difference. In addition, patients were clinically stable, in that they were able to elicit an $FEV_1 \geq 25\%$, but $\leq 85\%$ predicted value at Screening, had a positive sputum specimen (or throat swab) for *P. aeruginosa* at Screening and a history of at least 1 additional sputum culture positive for *P. aeruginosa* within the previous 12 months, and had received at least three 28-day courses or a total of 84 days of an inhaled tobramycin over the previous 12 months, with at least a 14-day course completed within 29 to 56 days prior to Visit 1 (Day 1).

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Test Product, Dose and Mode of Administration, Lot Number: MP-376 was administered by the inhalation route using the MP-376-customized PARI eFlow® nebulizer at a dose of 240 mg BID, approximately 8 to 12 hours apart. The dose refers to the dose of levofloxacin that was loaded into the nebulizer.

MP-376 Inhalation Solution, 100 mg/mL sterile water [redacted] was provided in single-use polyethylene ampules (2.4 mL) ready for administration. The dose was administered as 1 ampule BID.

Duration of Treatment: Three 56-day cycles (28 days on treatment and 28 days off treatment).

Reference Therapy, Dose and Mode of Administration, Batch Number: TIS was administered by the inhalation route using the PARI LC® PLUS nebulizer with compressor or via another nebulizer compatible with country-specific labeling at a dose of 300 mg BID, approximately 8 to 12 hours apart.

TIS ([redacted]) was provided in single-dose, ready-to-use ampules containing 300 mg of tobramycin. The dose was administered as one ampule BID.

Criteria for Evaluation:

Efficacy: Efficacy was evaluated by pulmonary function tests (PFTs); microbiologic assessment of sputum samples; the time to an exacerbation of CF lung disease, with exacerbations determined using the Respiratory and Systemic Symptoms Questionnaire (RSSQ) and by the independent Blinded Exacerbation Adjudication Committee; administration of systemic and/or inhaled antipseudomonal antimicrobials; and patient-reported outcomes (the Cystic Fibrosis Questionnaire – revised [CFQ-R]). Also evaluated were proportion of patients hospitalized; time to hospitalization; proportion of patients who missed at least 1 day of school, work, or a scheduled activity; time to first missed day of school, work, or a scheduled activity; and change in weight.

The primary efficacy endpoint was relative change in FEV_1 percent predicted from Baseline to Day 28. If non-inferiority was demonstrated by the lower limit of the 2-sided 95% confidence interval (CI) of the difference in means (MP-376 minus TIS) being greater than -4.0, then assessment of superiority of MP-376 compared to TIS would be performed for the endpoints of relative change and absolute change in FEV_1 percent predicted from Baseline to Day 28.

The secondary efficacy endpoints included the following:

- Pulmonary function:
  - Absolute and percent change in FEV_1 (L) from Baseline to Day 28
  - Absolute and relative change in FEV_1 percent predicted from Baseline by visit for all other scheduled study visits at which PFTs were collected

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- Absolute and relative change in FEV_1 percent predicted from Baseline to the average of Days 28, 84, and 140
- Absolute and percent change in forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25-75}, in L/s) from Baseline to Day 28.
- Absolute and percent change in forced vital capacity (FVC, in L) from Baseline to Day 28.
- Categorical assessment of percent change in FEV_1 (L) and relative change in FEV_1 percent predicted from Baseline to Day 28
- Categorical assessment of absolute change in FEV_1 (percent predicted) from Baseline to Day 28

- Microbiology
  - Change in *P. aeruginosa* density (log_{10} colony-forming units [CFU] per gram sputum) from Baseline to Day 28. Samples from throat swabs were not used for this endpoint.
  - Categorical assessment of change in *P. aeruginosa* density (log_{10} CFU per gram sputum) from Baseline to Day 28,
- Patient-reported outcomes
  - Change in the Respiratory Domain of the CFQ-R from Baseline to Day 28
  - Categorical assessment of change in the Respiratory Domain of the CFQ-R from Baseline to Day 28
- Clinical
  - Time (in days) to first exacerbation observed between Baseline and the Final Visit. A patient was defined as meeting this endpoint at the earliest date of any of the following events: concurrently met at least 4 of the 12 symptoms/signs that made up the modified Fuchs definition of an exacerbation; death; or receipt of an antipseudomonal agent for an event that did not meet modified Fuchs criteria but was determined to be an exacerbation for the purposes of the primary endpoint by the Blinded Exacerbation Adjudication Committee.
  - Time (in days) to administration of other systemic and/or inhaled antipseudomonal antimicrobials between Baseline and the Final Visit
  - Time to first hospitalization (in days) between Baseline and the Final Visit

[redacted].

- [redacted]
  - [redacted]

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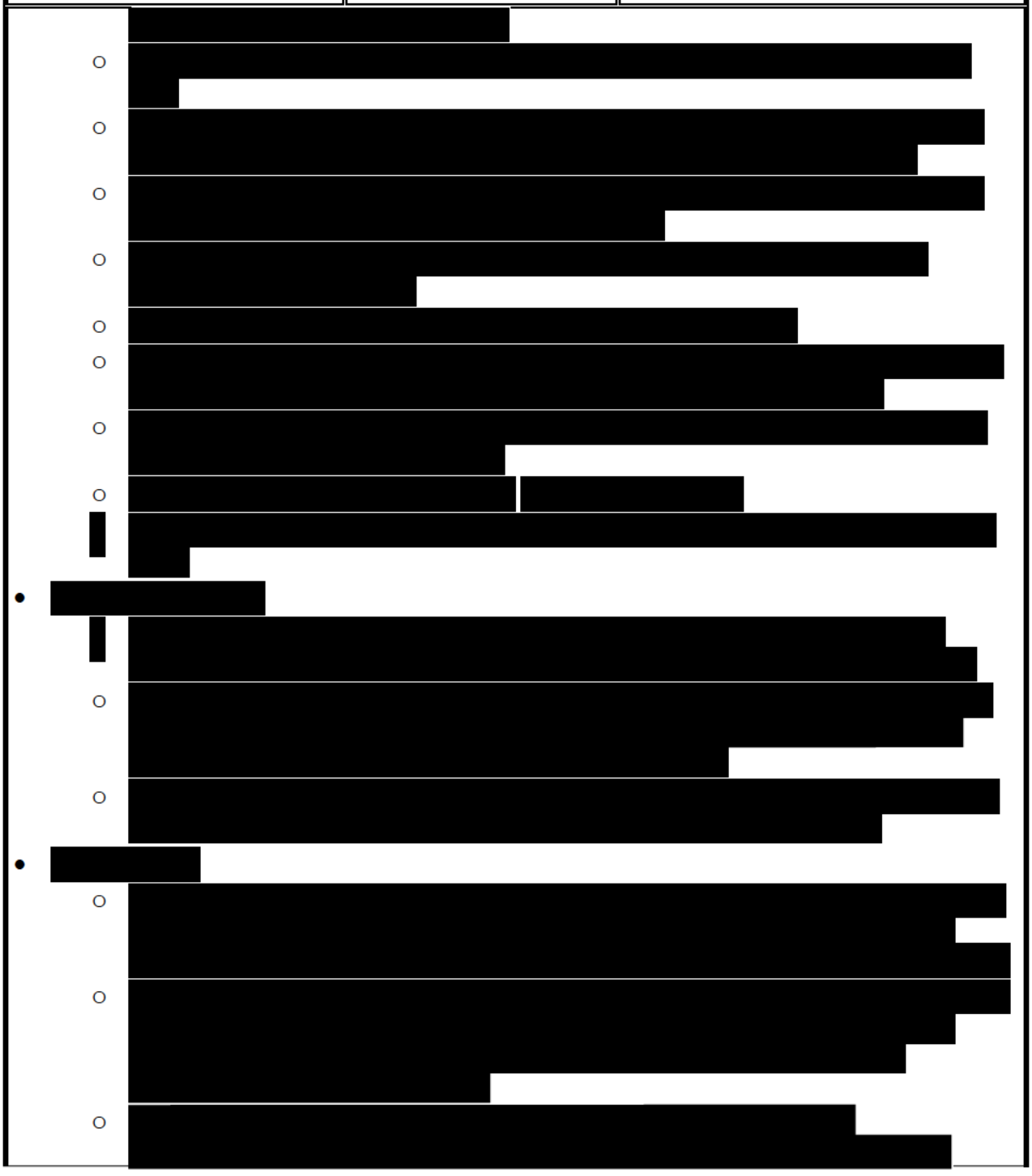

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Safety: Safety was assessed by evaluating treatment-emergent adverse events (TEAEs) and changes from Baseline in clinical laboratory evaluations, vital signs, physical examination findings, PFTs at Visit 1, electrocardiograms (ECGs), and RSSQ signs and symptoms.

Pharmacokinetics: Patient blood and sputum samples were obtained for the measurement of levofloxacin concentration. Serum PK samples were collected within 60 minutes (+ 10 minutes) prior to the start of dosing at Visits 2, 4, and 6. Post-dose serum and sputum PK samples were collected between 30 and 120 minutes after the start of nebulization at Visits 2 and 6.

Statistical Methods:

Efficacy:

The study protocol included prospectively defined methods for data analysis, which were further described and refined in a formal Statistical Analysis Plan finalized before the study database was locked and the data unblinded.

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The primary efficacy analysis was based on the ITT population. Additional supportive efficacy analyses were performed using the EE28 and EE140 populations. For primary and secondary efficacy analyses, missing values at Day 28 were imputed using the last observation carried forward (LOCF). For sensitivity analyses, missing values at Day 28 were imputed using other imputation methods.

For the primary analysis, comparison of relative change in FEV_1 percent predicted from Baseline to Day 28 was performed using an analysis of covariance (ANCOVA) model that included terms for: treatment group (MP-376, TIS), geographic region (US, non-US), age (12 to 18 years, > 18 years), and Baseline FEV_1 percent predicted (< 55%, ≥ 55%). An unstructured covariance matrix was used in the ANCOVA. The assessment of non-inferiority was based on the lower limit of the 2-sided 95% CI of the difference in means (MP-376 minus TIS). If the lower limit of this CI was greater than -4.0, then non-inferiority would be demonstrated. If non-inferiority was demonstrated, an assessment of superiority for both relative change and absolute change in FEV_1 percent predicted from Baseline to Day 28 would be performed using a 2-sided test at the 5% level of significance.

The secondary analyses of the change and percent change from Baseline to Day 28 in quantitative endpoints were completed using ANCOVA models including terms for treatment group, geographic region, age, Baseline FEV_1 percent predicted, and Baseline value for each specific endpoint as a covariate. The comparison of absolute and relative change in FEV_1 percent predicted from Baseline to the average of Days 28, 84, and 140 was performed using an ANCOVA model including terms for treatment group, geographic region, age, and Baseline FEV_1 percent predicted.

Secondary endpoints of absolute and relative change in FEV_1 percent predicted from Baseline to all other scheduled study visits at which PFTs were collected were analyzed using linear mixed models for repeated measurements. These models included fixed effects for treatment group, time, treatment group by time interaction, and geographic region, age, and Baseline FEV_1 percent predicted.

Ordered categorical assessments were analyzed using the Cochran-Mantel-Haenszel mean score test (assuming equally spaced scores for the levels of the endpoint) stratified by geographic region, age, and Baseline FEV_1 percent predicted.

The distributions of the time to exacerbation, time to administration of systemic and/or inhaled antipseudomonal antimicrobials, and time to first hospitalization in the 2 groups were compared using a 2-sided stratified (geographic region, age, and Baseline FEV_1 percent predicted) log-rank test. The distributions in the 2 groups were summarized using the Kaplan-Meier method. The estimated hazard ratio (HR) and 95% CI were obtained from a Cox proportional hazards regression model including terms for treatment (MP-376, TIS), geographic region, age, and

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Baseline FEV_1 percent predicted.

Safety: Safety analyses were conducted on the Safety population using descriptive statistics.

Pharmacokinetics: A population PK model of serum and sputum levofloxacin concentration-time data was performed. The analysis included a base model developed from previous clinical studies using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S-ADAPT. An iterative approach was taken to compare the serum and sputum concentrations obtained during sampling with the existing model. The results of the PK analyses are presented in a separate report.

SUMMARY – CONCLUSIONS

Disposition:

Two hundred eighty-two patients were randomized, 189 to MP-376 and 93 to TIS. All patients except 10 who were randomized (7 to MP-376, 3 to TIS) received at least 1 dose of Study Drug. Disposition was similar between the treatment groups; 87.8% of MP-376 and 89.2% of TIS patients completed the study. The primary reason for study discontinuation was an AE for 3.2% of MP-376 and 1.1% of TIS patients, withdrawal of consent for 1.1% of MP-376 and 1.1% of TIS patients, lost to follow-up for 0.5% of MP-376 patients, and "other" for 7.4% of MP-376 and 8.6% of TIS patients. There was no statistically significant difference in the distribution of time to study discontinuation between MP-376 and TIS (HR = 1.19; 95% CI: 0.92, 1.54). The mean number of days on study was 155.1 for the MP-376 group and 160.0 for the TIS group.

A similar proportion of patients in each treatment group permanently discontinued Study Drug, 12.7% of MP-376 and 15.1% of TIS patients. The primary reason for permanent discontinuation of Study Drug was an AE for 6.3% of MP-376 and 1.1% of TIS patients, starting antimicrobial agents for 1.6% of MP-376 and 5.4% of TIS patients, patient decision for 3.2% of MP-376 and 4.3% of TIS patients, Investigator decision for 0.5% of MP-376 and 1.1% of TIS patients, and "other" for 1.1% of MP-376 and 3.2% of TIS patients. Fifteen MP-376 patients and 7 TIS patients both permanently discontinued Study Drug and were discontinued from the study.

Demographics:

The treatment groups were similar in demographic characteristics. In the Safety Population, age ranged from 12 to 63 years with a mean of 28.5 years and with 86.4% of patients over 18 years. Weight ranged from 30.2 to 124.8 kg with a mean of 61.4 kg. Most of the patients were white (96.0%) and the majority were male (56.6%). The geographic distribution of patients was also similar between the treatment groups, with 68.8% in the US overall and the remainder in Europe and Israel.

Baseline characteristics were similar between the treatment groups. In the Safety population,

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mean FEV_1 and percent predicted FEV_1 overall were 2.01 L and 54.5%, respectively. Mean FVC and percent predicted FVC overall were 3.24 L and 73.0%, respectively. The mean number of inhaled antimicrobial courses during the previous year was 5.9, with 44.1% of patients having received 6 or more courses. The proportion of patients by Baseline infecting pathogen was similar between the treatment groups; the most frequent pathogen was *P. aeruginosa*, which was reported for 95.6% of patients in each treatment group.

The majority of patients, 68.5% of MP-376 and 62.2% of TIS patients, demonstrated at least 80% treatment compliance over the entire study.

Efficacy Results:

The results for key endpoints are summarized in the table below. Results are summarized here for the ITT population.

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Summary of Key Endpoints, Intent-to-Treat Population	**TIS 300 mg BID (N = 93)**	**MP-376 240 mg BID (N = 189)**	**MP-376 240 mg BID Compared to TIS**	**Favors**	**P-value**
Primary Endpoint: Relative change in FEV_1 percent predicted (Baseline to Day 28) LS mean (SE)[1]	0.38 (1.262)	2.24 (1.019)	LS mean difference (95% CI)[1] 1.86 (-0.66, 4.39)[2]	MP-376	0.1481[1]
Absolute change in FEV_1 percent predicted (Baseline to Day 28) LS mean (SE)[1]	0.20 (0.626)	1.24 (0.505)	LS mean difference (95% CI)[1] 1.04 (-0.21, 2.30)	MP-376	0.1015[1]
Log change in *P. aeruginosa* density (Log_{10} CFU/g sputum) (Baseline to Day 28) LS mean (SE)[1]	-1.19 (0.243)	-0.75 (0.196)	LS mean difference (95% CI)[1] 0.44 (-0.01, 0.88)	TIS	0.0530[1]
Change in Respiratory Domain of the CFQ-R (Baseline to Day 28) LS mean (SE)[1]	-1.31 (1.576)	1.88 (1.278)	LS mean difference (95% CI)[1] 3.19 (0.05, 6.32)	MP-376	0.0463[1]
Time to exacerbation (Baseline to final visit) Median days (95% CI)	90.5 (57, 135)	131 (106, 152)	Hazard ratio[3] 0.78 (0.57, 1.07)	MP-376	0.1542[4]
Time to need for inhaled or systemic anti-pseudomonal antimicrobials and meeting symptoms requirements Median days (95% CI)	110 (70, 141)	141 (123, 170)	Hazard ratio[3] 0.73 (0.53, 1.01)	MP-376	0.0396[4]

[1] Estimates were determined from an ANCOVA model with terms for treatment, region (US, non-US), age (12 to 18 years, > 18 years), Baseline FEV_1 (< 55%, ≥ 55%), and Baseline as a covariate. For comparison of FEV_1 percent predicted the Baseline covariate was not included in the model.

[2] The primary endpoint of non-inferiority of MP-376 relative to TIS for relative change from Baseline to Day 28 in FEV_1 percent predicted was met, based on the lower limit of the LS mean difference (MP-376 minus TIS) 95% CI being greater than the pre-specified non-inferiority margin of -4%.

[3] Estimates were obtained from a Cox proportional hazards regression model including terms for treatment, region (US, non-US), age (12 to 18 years, > 18 years), and Baseline FEV_1 (< 55%, ≥ 55%).

[4] P-value was determined using a log-rank test stratified by region (US, non-US), age (12 to 18 years, > 18 years), and Baseline FEV_1 (< 55%, ≥ 55%).

The primary endpoint of non-inferiority of MP-376 relative to TIS for relative change from Baseline to Day 28 in FEV_1 percent predicted was met based on the lower limit of the LS mean difference (MP-376 minus TIS) 95% CI of -0.66%, which was greater than the pre-specified non-inferiority margin of -4%. Non-inferiority was also demonstrated for the EE28 population with the lower limit of the LS mean difference 95% CI of -0.25%. The between-group difference numerically favored MP-376.

Favorable responses of MP-376 compared to TIS were demonstrated at the end of each

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treatment cycle for multiple endpoints among the PFTs, patient-reported outcomes, and clinical assessments.

The results consistently favored the MP-376 group numerically for the PFT endpoints at the end of each treatment period (Days 28, 84, and 140) and the between-group differences were in some cases statistically significant (with no multiplicity adjustments). The PFT endpoints evaluated included absolute change, percent or relative change, and categorical analysis for FEV_1 percent predicted, FEV_1 (L), FVC (L), and FVC percent predicted, and absolute and percent change for FEF_{25-75}.

The differences in distributions of time to need for inhaled or systemic antipseudomonal antimicrobials and meeting symptom requirements and time to need for inhaled or systemic antipseudomonal antimicrobials regardless of symptom requirements were statistically significant in favor of MP-376, and the estimated hazard ratio for the time to exacerbation numerically favored MP-376.

A statistically significantly lower proportion of MP-376 patients (17.5%) than TIS patients (28%) were hospitalized from Baseline to the Final Visit secondary to a worsening respiratory status (p=0.0432).

The decrease in *P. aeruginosa* sputum density was numerically larger in favor of TIS throughout the study.

The change in Respiratory Domain of the CFQ-R was statistically significant favoring MP-376 at the end of each treatment period (Days 28, 84, and 140).

Results from multiple subgroup analyses (by age group, race, geographic region, Baseline FEV_1 percent predicted category, courses of inhaled antimicrobial in the past year, number of exacerbations in the past year, and co-infection at Baseline) for the endpoints of absolute and relative changes in FEV_1 percent predicted, time to exacerbation, log change in *P. aeruginosa* sputum density, and change in CFQ-R Respiratory Domain did not reveal any trends that would change the overall efficacy conclusions drawn from the study findings.

Safety Results:

With the exception of more treatment-related TEAEs in the MP-376 group during the treatment periods and the entire study and a higher proportion of TIS patients with SAEs, the safety profile was similar between the treatment groups, as summarized in the following table.

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Summary of Treatment-Emergent Adverse Events, Safety Population	**TIS 300 mg BID (N = 90)**	**MP-376 240 mg BID (N = 182)**
Patients reporting at least 1 TEAE during entire study	90 (100.0%)	180 (98.9%)
Patients reporting at least 1 TEAE during treatment periods	81 (90.0%)	170 (93.4%)
Patients reporting at least 1 treatment-related TEAE[1] during entire study	14 (15.6%)	81 (44.5%)
Patients reporting at least 1 treatment-related TEAE[1] other than dysgeusia during entire study	14 (15.6%)	55 (30.2%)
Patients reporting at least 1 treatment-related TEAE[1] during treatment periods	12 (13.3%)	81 (44.5%)
Patients reporting at least 1 treatment-related TEAE[1] other than dysgeusia during treatment periods	12 (13.3%)	53 (29.1%)
Patients reporting TEAE by highest severity during entire study		
Mild (Grade 1)	34 (37.8%)	60 (33.0%)
Moderate (Grade 2)	39 (43.3%)	98 (53.8%)
Severe (Grade 3)	17 (18.9%)	22 (12.1%)
Life-threatening (Grade 4)	0	0
Death (Grade 5)	0	0
Patients reporting at least 1 SAE during entire study	29 (32.2%)	40 (22.0%)
Patients reporting at least 1 SAE during treatment periods	15 (16.7%)	11 (6.0%)
Patients discontinuing study due to an AE[2]	1 (1.1%)	6 (3.3%)
Patients discontinuing Study Drug due to an AE[2,3]	6 (6.7%)	15 (8.2%)

Entire study = on and off Study Drug, treatment periods = Days 1 to 28 of each cycle, inclusive

[1] Treatment-related events included all events reported with "possible" or "probable" relationship to Study Drug.

[2] Patients could be included in both discontinuation from study and Study Drug categories.

[3] Includes patients who started antimicrobial agents for worsening respiratory symptoms or an exacerbation.

MP-376 was safe and well tolerated in a population of patients with extensive prior TIS experience when administered BID over 3 consecutive 56-day cycles (28 days on treatment and 28 days off treatment). Most patients in both treatment groups had TEAEs during the treatment periods. With the exception of dysgeusia, which was only reported in the MP-376 group, the nature of the TEAEs was similar between the treatment groups during the treatment periods and the entire study. The only apparent adverse reactions specific to the inhaled route of administration of levofloxacin (e.g., dysgeusia, cough, increased respiratory secretions) were typically mild, reversible, and uncommonly prompted a permanent cessation of Study Drug.

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Excluding disease progression of CF pulmonary disease, which represents a pulmonary exacerbation, the other most frequent TEAEs were cough, sputum increased, respiratory tract congestion, increased viscosity of bronchial secretion, fatigue, and weight decreased. During the treatment periods, the TEAEs other than dysgeusia that were reported for at least 5.0% more MP-376 patients than TIS patients were cough, sputum increased, paranasal sinus hypersecretion, and sinus headache. Blood glucose increased was reported for at least 5.0% more TIS than MP-376 patients. Among the most common TEAEs over the entire study, the TEAEs other than dysgeusia that were reported for at least 5.0% more MP-376 than TIS patients were sputum increased and paranasal sinus hypersecretion. Weight decreased was at least 5% more common in the TIS group than the MP-376 group.

Most of the TEAEs during the study were mild or moderate; no deaths or life-threatening TEAEs were reported.

TEAEs were considered by the Investigator to be at least possibly related to Study Drug for 44.5% of MP-376 patients and 13.3% of TIS patients during the treatment periods and 44.5% of MP-376 patients and 15.6% of TIS patients during the entire study. Treatment-related dysgeusia was reported for 25.3% of MP-376 patients during the treatment periods and the entire study. Other than dysgeusia, the most frequently reported treatment-related TEAEs (reported for over 5% of patients in either group) were cough and sputum increased.

The younger subgroup (12 to 18 years) included 12 TIS and 26 MP-376 patients and the older subgroup (> 18 years) included 78 TIS and 157 MP-376 patients. Among the most frequently reported TEAEs, cough, sputum increased, increased viscosity of bronchial secretion, and paranasal sinus hypersecretion had an increased incidence (at least 5.0% difference) in the younger subgroup receiving MP-376 compared with the older subgroup receiving MP-376 during both the treatment periods and the entire study. The incidence of weight decreased was greater in the younger subgroup compared with the older subgroup receiving TIS during the treatment periods, and of note, there was an imbalance between treatment groups in decreased weight over the entire study (28.0% MP-376 versus 41.7% TIS) in the 12 to 18 year age group. In addition, cough, sputum increased, respiratory tract congestion, increased viscosity of bronchial secretion, paranasal sinus hypersecretion, and pyrexia had an increased incidence in the younger subgroup receiving TIS during the entire study.

Excluding disease progression, treatment-emergent SAEs were reported for 7.7% of MP-376 and 14.4% of TIS patients.

TEAEs led to discontinuation of the study for 3.3% of MP-376 patients and 1.1% of TIS patients; these events were disease progression (1.1% in each treatment group), dysgeusia (1.1% MP-376), hemoptysis (0.5% MP-376), and respiratory tract congestion (0.5% MP-376). The proportion of patients who permanently discontinued Study Drug due to TEAEs was 8.2% in the

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MP-376 group (including 2.2% due to disease progression and 1.6% due to dysgeusia) and 6.7% in the TIS group (including 4.4% due to disease progression).

There was a greater proportion of patients with TEAEs of disease progression as well as more SAEs of disease progression and more discontinuations due to disease progression in TIS patients than MP-376 patients; however the incidence of disease progression in the subgroup of patients 12 to 18 years old was similar in TIS and MP-376 patients.

Fluoroquinolone class effects associated with systemic administration, such as tendon, eye, and cardiac events, were uncommon in this study. No TEAEs were reported in this study that were related to myasthenia gravis, severe cutaneous adverse reactions, acute renal failure, torsade de pointes/QT prolongation, convulsions, peripheral neuropathy, psychosis/psychotic disorders, ocular toxicity (e.g., retinal detachment), or *Clostridium difficile*-associated diarrhea/pseudomembranous colitis. Hepatic enzyme-related TEAEs were reported for 2.7% of MP-376 and no TIS patients; none of these events was an SAE or led to discontinuation of the study or Study Drug. The incidence of arthralgia was low and similar between treatment groups (5.5% of MP-376 patients and 5.6% TIS), and there were 6 additional cases of arthropathy, arthritis, costochondritis, or tendonitis in the MP-376 group. One MP-376 patient had an SAE of costochondritis that led to discontinuation of Study Drug and resolved after treatment, while another MP-376 patient had tendonitis; there were no reports of tendon rupture in this study. Blood glucose increased or hyperglycemia was reported for 2.7% of MP-376 and 7.8% of TIS patients, most of whom had a prior history of diabetes mellitus or impaired glucose tolerance at Baseline, while blood glucose decreased or hypoglycemia was reported for 2.7% of MP-376 and no TIS patient. None of these dysglycemia events was symptomatic, an SAE, or led to discontinuation of the study or Study Drug.

With the exception of hepatic enzyme and glycemia-related TEAEs as noted above, no trends in laboratory parameter abnormalities during the study were observed. Laboratory-related TEAEs that were considered severe were reported for 1 MP-376 patient (asymptomatic with increased AST of 6.5 x ULN that was considered possibly related to Study Drug and resolved; hepatic enzymes were normal upon rechallenge during the third treatment period) and 1 TIS patient (anemia that was considered not related to Study Drug that occurred concurrently with TEAEs of malnutrition, disease progression, procedural pain, and epistaxis; was treated with transfusion of packed red blood cells; and resolved).

There were no clinically relevant changes in physical examinations, vital signs, or ECGs in either treatment group.

The mean change in FEV_1 from pre-dose to post-dose on Day 1 was similar between the treatment groups; 1 MP-376 patient had a decrease greater than 20%. A bronchodilator was used to prevent or alleviate symptoms related to Study Drug dosing at any time during the study

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by 0.5% of MP-376 and 1.1% of TIS patients.

For each of the RSSQ signs and symptoms categories, the most severe response was reported for a higher proportion of TIS patients compared with MP-376 patients. For most categories the proportion of patients with the worst response in both treatment groups remained stable or decreased from Day 28 to Day 140.

Pharmacokinetic Results: Results of the PK analyses are presented in a separate report.

CONCLUSIONS

Non-inferiority of MP-376 to TIS was demonstrated for the primary endpoint of relative change in FEV_1 percent predicted from Baseline to Day 28. Favorable responses of MP-376 compared to TIS were demonstrated at the end of each treatment period for multiple endpoints among the PFTs, patient-reported outcomes, and clinical assessments. MP-376 was safe and well tolerated in a population of patients with extensive prior TIS experience when administered BID over 3 consecutive 56-day cycles (28 days on treatment and 28 days off treatment). The only apparent adverse reactions specific to the inhaled route of administration of levofloxacin (e.g., dysgeusia, cough, increased respiratory secretions) were typically mild, reversible, and uncommonly prompted a permanent cessation of study medication.

Date of the Report: 28 June 2013