**Supplement**

Approved inhalational antimicrobials for use in people with CF and chronic P. aeruginosa infection in the EU are tobramycin (TOBI®, TOBI PodhalerTM, Bramitob®), colistimethate (ColoBreathe®, Promixin®), and aztreonam (Cayston®) and in the US are tobramycin (TOBI, TOBI Podhaler, Bethkis®) and aztreonam (Cayston).

**Additional Methods**

**Inclusion Criteria**

Female and male patients were to be included in the study if they met all of the following criteria:

- Were at least 12 years of age
- Weighed at least 30 kg or 66 pounds
- Had documentation of a CF diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and one or more of the following criteria:
    - sweat chloride ≥ 60 mEq/L by quantitative pilocarpine iontophoresis test
    - two well-characterized mutations in the CF transmembrane conductive regulator gene
    - abnormal nasal potential difference
- Were able to elicit an $FEV_1$ > 25% but < 85% predicted value at Screening based on Hankinson/National Health and Nutrition Examination Survey (NHANES) III criteria
- Must have had a sputum or throat swab (if unable to produce sputum) specimen at Screening positive for *P. aeruginosa* and a history of at least one additional sputum culture positive for *P. aeruginosa* within the last 12 months prior to Visit 1

- Must have 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
- Were clinically stable with no significant changes in health status within the last 28 days prior to Visit 1
- Were able to perform an acceptable spirometry session (defined as three acceptable or usable efforts per American Thoracic Society/European Respiratory Society [ATS/ERS] criteria) at Screening
- Had not smoked tobacco within 28 days prior to Visit 1 and agreed not to smoke for the duration of the study
- Were able to and had given written informed consent (if they were adults) or assent in combination with their legal representative(s) (if they were minors) in a manner approved by the IRB/IEC and were willing to comply with the requirements of the study

**Exclusion Criteria**

Patients were to be excluded from the study if they met any of the following criteria:

- Had used an investigational agent within 28 days prior to Visit 1
- Had used any nebulized or systemic antimicrobials active against *P. aeruginosa* within 28 days prior to Visit 1, other than maintenance oral azithromycin, which must have been initiated at least 28 days prior to Visit 1
- History of hypersensitivity or intolerance to fluoroquinolones (e.g., joint or tendon disorders) or any excipients of LIS (magnesium chloride)

- History of hypersensitivity or intolerance to inhaled or systemic aminoglycosides, including tobramycin or any excipients of TIS (sodium chloride, sulfuric acid, sodium hydroxide)
- History of intolerance to bronchodilators or unwilling to use a bronchodilator during the study
- Current use of oral corticosteroids in doses exceeding the equivalent of 10 mg prednisone/day or 20 mg prednisone every other day at Screening or Visit 1
- Changes in technique or schedule of physiotherapy and/or airway clearance techniques (ACT) within 14 days of Visit 1
- Changes in medical regimen for treatment of CF (e.g., introduction, dose escalation, or elimination of therapies such as dornase alfa, nonsteroidal anti-inflammatory drugs [NSAIDs], azithromycin, hypertonic saline, or inhaled corticosteroids) within 28 days of Visit 1
- History of lung transplantation
- Evidence of upper respiratory tract infection within 10 days or lower respiratory tract infection within 28 days prior to Visit 1
- Active treatment for allergic bronchopulmonary aspergillosis
- Active treatment for mycobacterial lung infection
- Were pregnant, breastfeeding, or unwilling to practice a highly effective method of birth control or abstinence during participation in the study (women only).
- Had a history of a seizure disorder requiring antiseizure medications (e.g., epilepsy)

- Known history of chronic infection with human immunodeficiency virus (HIV), or chronic active hepatitis secondary to hepatitis B and/or hepatitis C infection (based on medical history; screening laboratory tests were not required)
- Had a history of hemoptysis ≥ 30 mL over any 24-hour period during the 28 days prior to Visit 1
- Had a calculated creatinine clearance less than 20 mL/min (Cockroft-Gault method) at Screening for patients who were ≥ 18 years of age. Had a calculated creatinine clearance less than 20 mL/min/1.73 m2 (Schwartz method) at Screening for patients who were < 18 years of age.
- Had an oxygen saturation ≤ 90% on room air at Screening or Visit 1
- Had a > 15% relative change (increase or decrease) in $FEV_1$ (L) from Screening to Visit 1
- History of suspected auditory, vestibular, or neuromuscular dysfunction
- Had a present condition or abnormality in screening laboratory tests or physical examination findings that, in the opinion of the Investigator or Medical Monitor, would have compromised the safety of the patient or the quality of the data
- Were a dependent (as an employee or relative) of Mpex, CRO, or Investigator

**Randomization**

Randomization to treatment groups was achieved by an automated Interactive Voice Response System and was stratified by geographic region (US vs. non-US), age (12-18 years vs. >18 years) and by forced expiratory volume in one second (FEV1) percent predicted (< 55% vs. ≥55%).

**Primary Efficacy Endpoint**

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 (LIS minus TIS) being greater than -4.0, then assessment of superiority would be performed for the endpoints of relative change and absolute change in $FEV_1$ percent predicted from Baseline to Day 28; in that case these endpoints would be termed contingent endpoints.

**Pulmonary Function Testing**

All patients underwent standardized spirometry to determine their FVC, $FEF_{25-75}$, and $FEV_1$. Spirometry was performed and reviewed according to ATS and ERS Spirometry Standards (Miller et al, 2005), i.e., at least 3 PFT efforts had to meet ATS/ERS criteria as usable or acceptable for a spirometry session to be considered acceptable. All PFT results were reviewed by a designated centralized spirometry over-reader (Vitalograph, Buckingham, UK) who determined if a spirometry session was acceptable and which efforts were considered the best for $FEV_1$, FVC, and $FEF_{25-75}$ as outlined in the Spirometry Procedures Manual. Patients who did not have an acceptable spirometry session at Screening were not to be enrolled. After patients were enrolled, unacceptable spirometry was to be deemed a deviation.

**Pulmonary exacerbations**

To meet the definition of an exacerbation, patients must concurrently have had at least 4 of the 12 symptoms/signs as defined by Fuchs, died, or received an antipseudomonal agent for an event that did not meet the Fuchs criteria but was determined to be an exacerbation for the

purposes of the exacerbation endpoint by the independent Blinded Exacerbation Adjudication Committee.

The independent Blinded Exacerbation Adjudication Committee was formed and operated independently under its own charter. The committee reviewed information on patients who did not meet Fuchs criteria for an exacerbation but received treatment with anti-pseudomonal antimicrobial agents for an exacerbation or worsening respiratory symptoms during the study. The committee also reviewed information on patients who met Fuchs criteria and were not prescribed anti-pseudomonal antimicrobial agents. The committee determined in a blinded fashion whether the described symptoms, signs, and other information provided in a narrative by the Principal Investigator should have been classified as an exacerbation.

**Cystic Fibrosis Questionnaire Revised (CFQ-R)**

The CFQ-R is a disease-specific instrument that measures health-related quality of life for adolescents and adults with CF. It consists of multiple questions with generic and disease-specific scales. The CFQ-R was administered per instructions in the Study Operations Manual during Visits 1, 2, 3, 4, and Final Visit. Three versions of the CFQ-R were used in this study based on the age of the patient: patients 14 years and older, patients 12 to 13 years old, and a parent/caregiver questionnaire for patients 6 to 13 years old. The versions are slightly different in that not all of the questions are included in each version and some of the questions are worded differently. For patients 13 years and younger, both the child and parent versions were completed and where a domain score was calculated from both versions, the domain score for the parent version was used in the analysis. The average score of the questions associated with each domain on each version was calculated and converted to a scale from 0 to 100 so the scores were

analyzed the same way across the versions. The CFQ-R was the first assessment performed at all visits when it was collected.

**Other Efficacy Endpoint Analyses**

All other endpoint analyses were conducted using the ITT populations. The 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 (LIS, TIS), geographic region (US, non-US), age (12 to 18 years, > 18 years), Baseline FEV1 percent predicted (< 55%, ≥ 55%), and Baseline value 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 (LIS, TIS), geographic region, age, and Baseline $FEV_1$ percent predicted. Other endpoints of absolute and relative change in $FEV_1$ percent predicted from Baseline by visit for 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 (LIS, TIS), geographic region, age, and Baseline $FEV_1$ percent predicted.

**Time to Study Discontinuation and Permanent Study Drug Discontinuation**

There was no statistically significant difference in the distribution of time to study discontinuation between LIS and TIS (HR = 1.19; 95% CI: 0.92, 1.54; p=0.30). The mean number of days on study was 155.1 for the LIS group and 160.0 for the TIS group.

## Acknowledgments

### List of Investigators

### USA

Daniel Brown (University of South Carolina - School of Medicine, Columbia, SC); Kevin Shaw (University of California, San Diego, La Jolla, CA); Patrick Flume (Medical University of South Carolina, Charleston, SC); Floyd Livingston (Nemours Children's Clinic Research, Orlando, FL); David Geller (Nemours Children's Clinic Research, Orlando, FL) Ted Liou (University of Utah Health Sciences Center, Salt Lake City, UT); Pedro Sepulveda (Alamo Clinical Research Cystic Fibrosis Center, San Antonio, TX); Adupa Rao (University of Southern California, Los Angeles, CA); Santiago Reyes (Oklahoma City, OK); Jonathan Rosen (Albany Medical College, Albany, NY); Bruce Trapnell (Cincinnati Children's Hospital Medical Center, Cincinnati, OH); Rodolfo Amaro (University of Texas Health Center at Tyler, Tyler, TX); Steven Boas (Chicago CF Care Specialists, Glenview, IL); Allen Dozor (New York Medical College, Valhalla, NY); Stanley Fiel (Morristown Memorial Hospital, Morristown, NJ); Bruce Nickerson (CHOC Hospital, Orange, CA); Gregory Shay (Kaiser Permanente – Northern California Kaiser Cystic Fibrosis Center, Oakland, CA); Thomas Keens, Arnold Platzker (Children's Hospital of Los Angeles, Los Angeles, CA); Lawrence Sindel (Mobile, AL); Jeffrey Hoag (Drexel University College of Medicine; Philadelphia, PA); Robert Fink (Dayton Children's Medical Center, Dayton, OH); Michael Ober (Indiana University, Indianapolis, IN); Aruna Sannuti (Indiana University, Indianapolis, IN); Brian Morrissey (University of California, Davis School of Medicine, Sacramento, CA); Peggy Radford (Phoenix Children's Hospital, Phoenix, AZ); Samya Nasr (University of Michigan-Women's Hospital, Ann Arbor, MI); Arvey Stone (Lutheran General Hospital, Niles, IL); Cori Daines (University of Arizona, Tucson, AZ); Gregory Sawicki (Children's Hospital Boston; Boston, MA); Christopher Oermann (Baylor College of Medicine, Houston, TX); Jonathan Spahr (Children's Hospital of Pittsburgh, Pittsburgh, PA); James Royall (University of Health Science Center, Oklahoma City, OK); Ronald Morton (University of Louisville; Louisville, KY); Dennis Stokes (University of Tennessee / LeBonheur Children's Medical Center, Memphis, TN); Craig Nakamura (Childrens Lung Specialists of Nevada, Las Vegas, NV); Joanne Billings (University of Minnesota, Minneapolis, MN); Matthias Salathe (University of Miami School of Medicine, Miami, FL); Laura Sass (Eastern Virginia Medical School, Norfolk, VA); Philip Black (Children's Mercy Hospital & Clinics, Kansas City, MO); Mark Pain (Rady Children's Hospital San Diego, San Diego, CA); Nathan Kraynack (Children's Hospital Medical Center of Akron, Akron, OH); Ibrahim Abdulhamid (Wayne State University, Detroit, MI); Ronald Williams (VCU Health System-Medical College of Virginia, Richmond, VA); Paul Comber (Albany Medical College, Albany, NY); Mark Rolfe (Tampa General Hospital, Tampa, FL); Gwendolyn Sue Kerby (The Children's Hospital, Aurora, CO); David Nichols (National Jewish Health Adult Cystic Fibrosis Center, Denver, CO); Dion Roberts (Providence Health Systems, Anchorage, AK); Carolyn Cannon (UT Southwestern Medical Center, Dallas, TX); Terry Chin (Miller Children's Hospital, Long Beach, CA); Magdalen Gondor (All Children's Hospital; St Petersburg, FL); Bennie McWilliams (Austin, TX); Aaron Chidekel (Alfred I. duPont Hospital for Children, Wilmington, DE); David Schaeffer (Nemours Children's Clinic Research, Jacksonville, FL); Susan Millard (Helen DeVos Women and Children's Center, Grand Rapids, MI); Michael Anstead (University of Kentucky, Lexington, KY); Jeff Atkinson (Washington University, St Louis, MO); Bruce Barnett (Toledo Children's Hospital, Toledo, OH); Dorothy Bisberg (Saint

Barnabas Pediatric Pulmonary & CF Center, Livingston, NJ); Perry Brown (St Luke's CF Center of Idaho, Boise, ID); Lea Davies (University of New Mexico, Albuquerque, NM); Maria Riva (Via Christi-St Francis CF Clinic, Wichita, KS); Ronald Gibson (Seattle Children's, Seattle, WA); Denis Hadjiliadis (University of Pennsylvania, Philadelphia, PA); Gregory Montgomery (Riley Hospital for Children, Indiana University, Indianapolis, IN); Claire Keating (Columbia University Medical Center, New York, NY); Dana Kissner (Wayne State University, Detroit, MI); Peter Konig (University of Missouri, Columbia, MO); Laurie Leclair (Vermont Lung Center, Colchester, VT); Craig Lapin (Hartford Hospital Connecticut, Hartford, CT); Adrienne Prestridge (Children's Memorial Hospital, Chicago, IL); Suzanne Miller (University of Mississippi Medical Center, Jackson, MS); Kathyrn Moffett (West Virginia University, Morgantown, WV); Samuel Moskowitz (Mass General Hospital CF Center, Boston, MA); Peter (Jim) Murphy (University of Nebraska Medical Center, Omaha, NE); Edward Naureckas (University of Chicago Hospitals, Chicago, IL); Julie Noe (Children's Hospital of Wisconsin, Milwaukee, WI); Worth Parker (Dartmouth Hitchcock Medical Center – Lebanon, Lebanon, NH); Dr Deborah Froh (University of Virginia Children's, Charlottesville, VA); Mark Robbins (University of Virginia, Charlottesville, VA); Michael Schechter (Emory University School of Medicine, Atlanta, GA); Karen Schultz (Cook Children's Medical Center, Fort Worth, TX); James Sexton (SUNY Upstate Medical University, Syracuse, NY); Gavin Graff (Penn State Milton S. Hershey Medical Center, Hershey, PA); Robert Vender (Penn State Milton S. Hershey Medical Center, Hershey, PA); Patricia Walker (Beth Israel Medical Center, New York, NY); James Wallace (Sanford Children's Specialty Clinic, Sioux Falls, SD); Elisabeth Willers (Vanderbilt University & Children's Hospital, Nashville, TN); Pamela Zeitlin (John Hopkins University, Baltimore, MD); Jonathan Zuckerman (Maine Medical Center, Portland, ME); Pamela Hofley (Dartmouth Hitchcock Medical Center-Manchester, Manchester, NH); Jalayne Lapke (OSF Saint Francis Medical Center, Peoria, IL); Julie Biller (Froedtert Hospital, Milwaukee, WI); Rubin Cohen (Long Island Jewish Medical Center, New Hyde Park, NY); Judith Voynow (Duke University Medical Center, Durham, NC); Marie Egan (Yale University School of Medicine, New Haven, CT); Paula Anderson (University of Arkansas for Medical Sciences, Little Rock, AR); Matasim Abu-Hasan (University of Florida at Shands, Gainesville, FL); Gopal Allada (Oregon Health and Sciences University; Portland, OR)

**Israel**

Eitan Karem (Hadassah Medical Center, Jerusalem); Lea Bentur (Rambah Medical Center, Haifa); Hannah Blau (Schneider Children's Medical Center of Israel, Petach Tikva); Ori Efrati (Sheba Medical Center, Ramat Gan)

**France**

Raphael Chiron (CRCM adultes et enfants, Montpellier); John Michael Fayon (Hôpital Pellegrin Enfants, Bordeaux); Isabelle Sermet-Gaudelus (Hôpital Necker-Enfants Malades, Paris); Isabelle Fajac (Hôpital Cochin, Paris); Marlene Murris-Espin (Hôpital Larrey-CHU de Toulouse, Toulouse); Pierre-Olivier Girodet (Hôpital Haut-Lévêque, Pessac)

**Germany**

Doris Stabb (Charité Campus Virchow-Klinikum, Berlin); Joachim Riethmuller (Universitätsklinik für Kinder- und Jugendmedizin, Tübingen); Rainald Fischer (Ludwig-Maximilians Universität Klinikum Innenstadt, München); Burkhard Bewig (Universitätsklinikum Kiel, Kiel); Wolfgang Gleiber (Universitätsklinikum Frankfurt, Frankfurt); Lutz Nahrlich (Universitätsklinik Gießen und Marburg GmbH Zentrum für Kinderheilkunde und Jugendmedizin Mukoviszidose-Zentrum Gießen, Gießen); Matthias Kappler, (von Haunersches Kinderspital der Universität München , Munich); Hans Eberhard Heuer (Kinderärztliche Gemeinschaftspraxis , Hamburg); Uwe Mellies (Universitätsklinikum Essen Zentrum für Kinder- und Jugendmedizin, Essen); Jutta Hammermann (Universitätskinderklinik Dresden Mukoviszidose-Ambulanz, Dresden); Joachim Bargon (Katharina-Kasper Kliniken GmbH, Frankfurt)

**Ireland**

Michael O'Mahony (Galway University Hospital, Galway); Paul McNally (Our Lady's Children's Hospital, Dublin); Professor Gerry McElvaney (Beaumont Hospital, Dublin)

**United Kingdom**

Stuart Elborn (Belfast City Hospital, Belfast); Alyn Morice (Castle Hill Hospital, Cottingham, East Yorkshire); David Honeybourne (Birmingham Heartlands Hospital, Birmingham); Ian Ketchell (University Hospital Llandough, Penarth, Cardiff); Daniel Peckham (St James's University Hospital, Leeds); Caroline Elston (King's College Hospital, London)

**Figure legends**

Figure 1. LS Mean relative change from baseline in CFQ-R Respiratory Domain scores by treatment group. Solid circles and lines denote LIS, open circles and dashed lines denote TIS. Bars represent standard errors. Sample sizes are provided in parentheses.

Figure 2. Proportions of patients for which the levofloxacin MIC of their most levofloxacin-resistant *P. aeruginosa* isolate increased, decreased, or remained unchanged from baseline to the end of the study. Patients randomized to receive TIS are shown in gray bars; LIS in black bars. The difference in patients with an increased levofloxacin MIC of their most resistant isolate was not significant (P =0.500)

flume desktop 20/10/2014 22:03
**Deleted:** TIS

**Tables**

Table 1: Highest MIC (µg.mL) per Patient of *P. aeruginosa* to Levofloxacin, Intent-to-Treat Population

| Time Point | TIS (n=93) | LIS (n=189) |
|---|---|---|
| Baseline | | |
| Number of isolates | 86 | 175 |
| Highest MIC > 1 µg/mL | 62 (72.1%) | 134 (76.6%) |
| Highest MIC > 2 µg/mL | 47 (54.7%) | 104 (55.0%) |
| $MIC_{50}$ | 4.0 | 4.0 |
| $MIC_{90}$ | 16.0 | 16.0 |
| Day 28 | | |
| Number of isolates | 79 | 159 |
| Highest MIC > 1 µg/mL | 60 (75.9%) | 133 (83.6%) |
| Highest MIC > 2 µg/mL | 48 (60.8%) | 115 (72.3%) |
| $MIC_{50}$ | 4.0 | 4.0 |
| $MIC_{90}$ | 16.0 | 32.0 |
| Day 140 | | |
| Number of isolates | 72 | 149 |
| Highest MIC > 1 µg/mL | 54 (75.0%) | 122 (81.9%) |
| Highest MIC > 2 µg/mL | 38 (52.8%) | 110 (73.8%) |
| $MIC_{50}$ | 4.0 | 8.0 |
| $MIC_{90}$ | 16.0 | 32.0 |
| Day 168/early termination | | |
| Number of isolates | 83 | 163 |
| Highest MIC > 1 µg/mL | 63 (75.9%) | 138 (84.7%) |
| Highest MIC > 2 µg/mL | 49 (59.0%) | 107 (65.6%) |
| $MIC_{50}$ | 4.0 | 4.0 |
| $MIC_{90}$ | 16.0 | 32.0 |

Patients were included only if they had *P. aeruginosa* at baseline. These included isolated form throat swab samples. Baseline was defined as the last non-missing value prior to first dose of Study Drug.

Table 2: Prior medications (Safety Population)

| Drug Class | TIS (n=90) | LIS (n=182) |
|---|---|---|
| Drugs for obstructive airways diseases | 84 (93.3%) | 168 (92.3%) |
| Inhaled short-acting β-agonists | 75 (83.3%) | 153 (84.1%) |
| Inhaled long-acting β-agonists | 49 (54.4%) | 89 (48.9%) |
| Inhaled anticholinergics | 15 (16.7%) | 31 (17.0%) |
| Inhaled corticosteroids | 51 (56.7%) | 95 (52.2%) |
| Dornase alfa | 73 (81.1%) | 133 (73.1%) |
| Hypertonic saline | 46 (51.1%) | 86 (47.3%) |
| Acetylcysteine | 10 (11.1%) | 14 (7.7%) |
| Pancreatic enzymes | 78 (86.7%) | 164 (90.1%) |
| Macrolides | 65 (72.2%) | 127 (69.8%) |
| Drugs for acid related disorders | 41 (45.6%) | 93 (51.1%) |
| Drugs used in diabetes | 22 (24.4%) | 54 (29.7%) |
| Ursodeoxycholic acid | 23 (25.6%) | 42 (23.1%) |
| Ibuprofen | 11 (12.2%) | 23 (12.6%) |
| Systemic corticosteroids | 5 (5.6%) | 11 (6.0%) |

Table 3: Pulmonary Function Test results ($FEV_1$), Intention to treat population

| $FEV_1$ (percent predicted), mean (SD) | | | | |
|---|---|---|---|---|
| | TIS (n=93) | LIS (n=189) | LS mean difference [95% CI] | P value |
| Baseline | 53.2 (15.7) | 54.8 (17.0) | | |
| Day 28 | 53.3 (16.2) | 56.0 (18.0) | | |
| Absolute change (Baseline to Day 28) | 0.1 (5.3) | 1.2 (4.8) | 1.04 [-0.21, 2.30] | 0.10 |
| Relative change (Baseline to Day 28) | 0.4 (11.8) | 2.3 (9.1) | 1.86 [-0.66, 4.39] | 0.15 |
| Day 56 | 52.6 (17.5) | 54.9 (17.1) | | |
| Absolute change (Baseline to Day 56) | -0.3 (5.8) | -0.7 (4.9) | -0.4 [-1.69, 1.00] | 0.61 |
| Relative change (Baseline to Day 56) | -0.9 (12.3) | -1.0 (9.7) | -0.1 [-2.86, 2.62] | 0.93 |
| Day 84 | 53.1 (17.5) | 56.9 (17.5) | | |
| Absolute change (Baseline to Day 84) | -0.2 (7.8) | 1.3 (4.3) | 1.6 [0.12, 3.09] | 0.03 |
| Relative change (Baseline to Day 84) | -0.2 (15.8) | 2.5 (8.7) | 2.96 [-0.03, 5.95] | 0.05 |
| Day 112 | 54.3 (17.3) | 55.1 (16.9) | | |
| Absolute change (Baseline to Day 112) | 0.5 (6.1) | -0.6 (5.5) | -0.7 [-2.21, 0.77] | 0.34 |
| Relative change (Baseline to Day 112) | 0.6 (12.4) | -0.8 (9.9) | -0.6 [-3.44, 2.25] | 0.68 |
| Day 140 | 53.4 (17.6) | 56.8 (17.6) | | |
| Absolute change (Baseline to Day 140) | 0.2 (7.0) | 1.0 (5.1) | 1.0 [-0.50, 2.49] | 0.19 |
| Relative change (Baseline to Day 140) | 0.3 (15.1) | 2.1 (10.0) | 2.1 [-1.01, 5.15] | 0.19 |
| Day 168 | 52.7 (17.7) | 54.9 (17.0) | | |
| Absolute change (Baseline to Day 168) | -1.5 (6.7) | -0.8 (5.2) | -0.3 [-1.74, 1.18] | 0.71 |
| Relative change (Baseline to Day 168) | -1.5 (14.8) | -1.2 (9.9) | 0.6 [-2.46, 3.57] | 0.72 |

Table 4: Pulmonary Function Test results (FVC), Intention to treat population

| FVC (percent predicted), mean (SD) | | | | |
|---|---|---|---|---|
| | TIS (n=93) | LIS (n=189) | LS mean difference [95% CI] | P value |
| Baseline | 71.7 (15.6) | 73.4 (15.5) | | |
| Day 28 | 71.0 (16.2) | 74.0 (16.4) | | |
| Absolute change (Baseline to Day 28) | -0.6 (5.5) | 0.6 (4.6) | 1.21 [-0.02, 2.44] | 0.05 |
| Relative change (Baseline to Day 28) | -0.8 (8.3) | 0.7 (6.8) | 1.48 [-0.37, 3.32] | 0.11 |
| Day 56 | 70.1 (17.0) | 73.6 (15.8) | | |
| Absolute change (Baseline to Day 56) | -1.1 (6.2) | -0.7 (5.1) | 0.4 [-1.04, 1.78] | 0.61 |
| Relative change (Baseline to Day 56) | -1.7 (9.5) | -0.9 (7.4) | 0.7 [-1.44, 2.78] | 0.53 |
| Day 84 | 69.8 (17.3) | 75.3 (16.3) | | |
| Absolute change (Baseline to Day 84) | -1.5 (8.3) | 1.1 (5.0) | 2.7 [1.01, 4.31] | 0.002 |
| Relative change (Baseline to Day 84) | -2.0 (11.5) | 1.5 (7.6) | 3.58 [1.19, 5.96] | 0.003 |
| Day 112 | 71.9 (17.0) | 73.8 (15.5) | | |
| Absolute change (Baseline to Day 112) | 0.3 (6.8) | -0.1 (5.8) | -0.5 [-2.14, 1.12] | 0.54 |
| Relative change (Baseline to Day 112) | 0.4 (9.8) | -0.6 (8.0) | -0.5 [-2.76, 1.85] | 0.70 |
| Day 140 | 70.2 (17.3) | 75.1 (16.3) | | |
| Absolute change (Baseline to Day 140) | -1.1 (8.2) | 0.7 (5.4) | 1.7 [0.01, 3.39] | 0.05 |
| Relative change (Baseline to Day 140) | -1.5 (11.9) | 1.0 (8.2) | 2.4 [-0.15, 4.85] | 0.07 |
| Day 168 | 70.7 (18.0) | 73.5 (15.5) | | |
| Absolute change (Baseline to Day 168) | -0.6 (8.0) | -0.7 (5.6) | -0.0 [-1.69, 1.64] | 0.98 |
| Relative change (Baseline to Day 168) | -1.3 (12.8) | -0.7 (7.8) | 0.6 [-1.92, 3.13] | 0.64 |

Table 5: Pulmonary Function Test results ($FEF_{25-75}$), Intention to treat population

| $FEF_{25-75}$ (L/s), mean (SD) | | | | |
|---|---|---|---|---|
| | TIS (n=93) | LIS (n=189) | LS mean difference [95% CI] | P value |
| Baseline | 1.09 (0.73) | 1.12 (0.74) | | |
| Day 28 | 1.12 (0.81) | 1.20 (0.85) | | |
| Absolute change (Baseline to Day 28) | 0.03 (0.28) | 0.09 (0.32) | 0.06 [-0.02, 0.13] | 0.15 |
| Percent change (Baseline to Day 28) | 2.7 (23.2) | 7.7 (22.1) | 4.97 [-0.65, 10.6] | 0.08 |
| Day 56 | 1.11 (0.79) | 1.14 (0.77) | | |
| Absolute change (Baseline to Day 56) | 0.01 (0.21) | -0.00 (0.28) | -0.01 [-0.08, 0.06] | 0.76 |
| Percent change (Baseline to Day 56) | 1.96 (22.2) | 1.68 (25.7) | -0.29 [-6.61, 6.03] | 0.93 |
| Day 84 | 1.14 (0.83) | 1.19 (0.77) | | |
| Absolute change (Baseline to Day 84) | 0.03 (0.33) | 0.06 (0.25) | 0.03 [-0.04, 0.10] | 0.41 |
| Percent change (Baseline to Day 84) | 4.03 (29.4) | 6.49 (20.6) | 2.76 [-3.39, 8.91] | 0.38 |
| Day 112 | 1.16 (0.82) | 1.13 (0.72) | | |
| Absolute change (Baseline to Day 112) | 0.03 (0.25) | -0.01 (0.30) | -0.03 [-0.10, 0.04] | 0.42 |
| Percent change (Baseline to Day 112) | 2.69 (24.4) | 1.59 (23.7) | -0.16 [-6.43, 6.10] | 0.96 |
| Day 140 | 1.16 (0.82) | 1.19 (0.78) | | |
| Absolute change (Baseline to Day 140) | 0.05 (0.31) | 0.05 (0.26) | 0.01 [-0.06, 0.09] | 0.71 |
| Percent change (Baseline to Day 140) | 4.50 (28.3) | 6.20 (22.5) | 2.47 [-3.88, 8.82] | 0.44 |
| Day 168 | 1.08 (0.74) | 1.14 (0.76) | | |
| Absolute change (Baseline to Day 168) | -0.02 (0.25) | -0.01 (0.29) | 0.02 [-0.05, 0.09] | 0.64 |
| Percent change (Baseline to Day 168) | -0.63 (25.3) | 0.84 (25.5) | 1.69 [-4.79, 8.16] | 0.61 |

Table 6: Change in *P. aeruginosa* Sputum Density ($log_{10}$ CFU/g sputum), Intention to treat population

| | TIS (n=93) | LIS (n=189) | LS mean difference [95% CI] | P value |
|---|---|---|---|---|
| Baseline | 7.15 (1.69) | 7.25 (1.62) | | |
| Day 28 | 6.28 (1.99) | 6.74 (1.90) | | |
| Absolute change (Baseline to Day 28) | -0.87 (1.76) | -0.51 (1.75) | 0.44 [-0.01, 0.88] | 0.05 |
| Day 56 | 6.82 (2.13) | 7.08 (1.84) | | |
| Absolute change (Baseline to Day 56) | -0.29 (2.07) | -0.16 (1.83) | 0.18 [-0.31, 0.68] | 0.47 |
| Day 112 | 6.65 (1.96) | 7.01 (1.74) | | |
| Absolute change (Baseline to Day 112) | -0.55 (1.57) | -0.28 (1.57) | 0.35 [-0.08, 0.78] | 0.11 |
| Day 140 | 6.12 (2.02) | 6.68 (1.88) | | |
| Absolute change (Baseline to Day 140) | -0.97 (2.12) | -0.52 (1.72) | 0.62 [0.12, 1.11] | 0.01 |
| Day 168 | 6.91 (1.80) | 7.11 (1.78) | | |
| Absolute change (Baseline to Day 168) | -0.25 (1.76) | -0.13 (1.62) | 0.18 [-0.24, 0.61] | 0.40 |